National Institute for Health and Care Excellence

Final

Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: diagnosis and management

[H] Appendices for the management of ME/CFS

NICE guideline NG206

Evidence reviews underpinning recommendations and research recommendations in the NICE guideline

October 2021

Final

These evidence reviews were developed by the National Guideline Centre

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Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Appendices Non-Pharmacological interventions

Appendix A Review protocols

Review protocol for non-pharmacological interventions

ID	Field	Content
	Scope	Management of ME/CFS
	Draft review question	3.2 What is the clinical and cost effectiveness of non-pharmacological interventions (such as diet and pacing) for people with ME/CFS?
0.	PROSPERO registration number	Not registered.
1.	Review title	What is the clinical and cost-effectiveness of non-pharmacological interventions for people with ME/CFS?
2.	Review question	What is the clinical and cost-effectiveness of non-pharmacological interventions for people with ME/CFS?
3.	Objective	To identify the most clinically and cost effective non-pharmacological methods to improve outcomes in adults and children with a diagnosis of ME/CFS.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Cinahl Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches:

		• Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review
5.	Condition or domain being studied	ME/CFS
6.	Population	Adults, children and young people who are diagnosed as having ME/CFS.

7.	Intervention/Exposure/Test	Any non-pharmacological treatments for the eligible population covered by RCTs. These can include (but are not restricted to):
		• Self-management
		  ○ Diaries
		  ○ Step counters (pedometers)
		  ○ Rest /convalescence
		  ○ Pacing
		  ○ Heart rate monitoring
		  ○ Adaptive Pacing Therapy
		• Aids/ adaptations / OT
		• Occupational/school advice
		• Behavioural/ Psychological support/ interventions
		  ○ NLP
		  ○ Counselling
		  ○ CBT
		  ○ Pragmatic rehab
		  ○ The Lightning Process
		  ○ Mindfulness
		  ○ Buddy/mentor programmes
		• Exercise interventions
		  ○ GET
		  ○ Physical rehabilitation
		• rTMS (repetitive transcranial magnetic stimulation)

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		• Compression socks
		• Hyperbaric O_2
		• Lifestyle advice. For example:
		  ○ Avoiding blue light
		• Relaxation techniques (ie Alexander Technique)
		• Dietary supplementation
		  ○ Co-enzyme Q10
		  ○ magnesium
		  ○ NADH
		  ○ Salt/saline
		  ○ vitamin D
		  ○ vitamin B12
		  ○ Fatty acids - omega 3 and 6
		  ○ multivitamin supplementation
		  ○ Iron
		  ○ Probiotics
		  ○ Pollen extract
		  ○ Medicinal mushrooms
		  ○ acclydine and amino acids
		  ○ acetyl-L-carnitine and propionyl-L-carnitine f
		  ○ alpha lipoic acid
		• Dietary strategies
		  ○ PEG feeding/ enteral feeding/ NG feeding
		  ○ Nutritional support
		  ○ Weight management
		  ○ Exclusion diets / FODMAPS (dermentable, oligosaccharides, disaccharides, monosaccharides and polyols)
		  ○ Dietary advice – healthy eating/balanced diet
		• Sleep interventions
		  ○ Sleep hygiene

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		○ CBTI • Pain management ○ TENS • Complementary therapies. For example: ○ Homeopathy ○ Massage ○ Osteopathy ○ Reflexology ○ Acupuncture ○ Acupressure ○ Yoga ○ Tai Chi Combinations of treatments (including combinations with pharmacological treatments) are allowed.
8.	Comparator/Reference standard/Confounding factors	• Each other • No treatment /wait list control / usual care • Sham/placebo/attention control
9.	Types of study to be included	• Randomised controlled trials • Systematic review of randomised controlled trials. For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will be used for citation searching. Non RCTs will not be considered as they will yield data that is at too high a risk of bias for decision-making. Cross-over RCTs will be considered if the wash-out period is deemed to be appropriate.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.

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11.	Context	N/A

12.	Primary outcomes (critical outcomes)	Longest follow up available:
		
		CRITICAL OUTCOMES:
		• Mortality
		• Quality of life (any validated scales). For example:
		  ○ SF36
		  ○ EQ5D
		• General symptom scales (any validated scales). For example:
		  ○ De Paul Symptom Questionnaire
		  ○ Self-Rated Clinical Global Impression Change Score
		• Fatigue/fatiguability (any validated scales). For example:
		  ○ Chalder fatigue Scale
		  ○ Fatigue Severity Scale
		  ○ Fatigue Impact scale
		• Physical functioning (any validated scales). For example:
		  ○ SF36 physical function
		  ○ SF36 PCS
		• Cognitive function (any validated scales). For example:
		  ○ MMSE
		• Psychological status (any validated scales). For example:
		  ○ Hospital Anxiety and Depression Scale
		  ○ Becks Depression Inventory
		• Pain (VAS/NRS)
		• Sleep quality (any validated scales). For example:
		  ○ Pittsburgh Sleep quality Index
		  ○ Epworth Sleepiness Scale
		  ○ Leeds Sleep Evaluation Questionnaire VAS
		• Treatment-related adverse effects
		• Activity levels – step counts

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		• Return to school / work
		• Exercise performance measures. For example:
		  ○ Hand grip
		  ○ Maximal Cycle Exercise Capacity
		  ○ 6 min walk
		  ○ Timed Up and Go
		  ○ 5 repetition sit to stand
		  ○ 40m walk speed
		  ○ Step test

13.	Secondary outcomes (important outcomes)	• Care needs • Impact on families and carers
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality-assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).

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15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Indirectness 1. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%.

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		2. The criteria used to diagnose people with CFS/ME should include post exertional malaise (PEM) as a compulsory feature. If the criteria does not include PEM the population will be downgraded for indirectness. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	<u>Stratification:</u> Age: children and young people vs adults Severity: severe vs moderate <u>Subgroups to investigate if heterogeneity is present</u> Interventions delivered by experienced (or specialist) CFS practitioners specifically designed for ME/CFS versus other interventions.
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English

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20.	Country	England		
21.	Anticipated or actual start date	01/01/20		
22.	Anticipated completion date	01/01/21		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☐
		Piloting of the study selection process	☑	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Dr Kate Kelley [Guideline lead] • Ms Maria Smyth [Senior systematic reviewer] • Ms Melina Vasileiou [Systematic reviewer] • Dr Richard Clubbe [Systematic reviewer]		

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		• Dr Karin van Bart [Systematic reviewer] • Mr David Wonderling [Health economist] • Ms Agnes Cuyas [Information specialist] • Ms Kate Ashmore [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10091
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	

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33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[534] **Inclusion and exclusion criteria**

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- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.

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	• Studies published in 2004 or later but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B Literature search strategies

This literature search strategy was used for the following review questions:

- What is the clinical and cost-effectiveness of non-pharmacological interventions for people with ME/CFS?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[534]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve.

Searches for patient views were run in Medline (OVID), Embase (OVID), CINAHL, and PsycINFO (ProQuest).

Table 1: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 June 2020	Exclusions
Embase (OVID)	1974 – 23 June 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 23 June 2020	None
PsycINFO (ProQuest)	Inception – 23 June 2020	Exclusions
Epistemonikos (The Epistemonikos Foundation)	Inception - 23 June 2020	None

Medline (Ovid) search terms

1.	Fatigue Syndrome, Chronic/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.

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8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language

Embase (Ovid) search terms

1.	chronic fatigue syndrome/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.

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8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	limit 33 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Fatigue Syndrome, Chronic] this term only
#2.	chronic* fatigue*:ti,ab
#3.	(fatigue* near/2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)):ti,ab
#4.	((myalgic or post infection* or postinfection*) near/1 (encephalomyelitis or encephalopathy)):ti,ab
#5.	((ME near/1 CFS) or (CFS near/1 ME) or CFIDS or PVFS):ti,ab
#6.	(Systemic Exertion Intolerance Disease or SEID):ti,ab
#7.	((CFS near/1 SEID) or (SEID near/1 CFS) or (ME near/1 CFS near/1 SEID) or (ME near/1 SEID) or (SEID near/1 ME)):ti,ab
#8.	(Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS)
#9.	((Post-exertional or postexertional) near/2 malaise):ti,ab

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#10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia):ti,ab
#11.	((atypical or simulating or resembling) near/1 poliomyelitis):ti,ab
#12.	((chronic epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis):ti,ab
#13.	xenotropic murine leukemia virus-related virus:ti,ab
#14.	effort syndrome*:ti,ab
#15.	((akureyri or iceland or tapanui or "royal free" or "royal free hospital") near/1 disease*):ti,ab
#16.	((yuppie or yuppy or tapanui) near flu):ti,ab
#17.	(or #1-#16)

CINAHL (EBSCO) search terms

S1.	(MH "Fatigue Syndrome, Chronic")
S2.	chronic* fatigue*
S3.	(fatigue* n2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*))
S4.	((myalgic or post infection* or postinfection*) and (encephalomyelitis or encephalopathy))
S5.	((ME and CFS) or (CFS and ME) or CFIDS or PVFS)
S6.	(Systemic Exertion Intolerance Disease or SEID)
S7.	((CFS and SEID) or (SEID and CFS) or (ME and CFS and SEID) or (CFS and ME and SEID) or (ME and SEID) or (SEID and ME))
S8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome) and (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion))
S9.	((Post-exertional or postexertional) n2 malaise)
S10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia)
S11.	((atypical or simulating or resembling) and poliomyelitis)
S12.	(chronic epstein Barr virus or chronic mononucleosis)
S13.	xenotropic murine leukemia virus-related virus
S14.	effort syndrome*
S15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) and disease*) or ((yuppie or yuppy or tapanui) and flu))
S16.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

PsycINFO (ProQuest) search terms

1.	((((chronic* fatigue*) OR (fatigue* NEAR2 (disorder* OR syndrome* OR post viral OR postviral OR immune dysfunction* OR post infection* OR postinfection*)) OR ((myalgic OR post infection* OR postinfection*) NEAR1 (encephalomyelitis OR encephalopathy)) OR ((ME NEAR1 CFS) OR (CFS NEAR1 ME) OR CFIDS OR PVFS) OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS NEAR1 SEID) OR (SEID NEAR1 CFS)) OR ((ME NEAR1 CFS NEAR1 SEID) OR (ME NEAR1 SEID) OR (SEID NEAR1 ME)) OR ((Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) NEAR6 (CFS OR chronic* fatigue* OR ME OR myalgic OR SEID OR systemic exertion)) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR ((atypical OR simulating OR resembling) NEAR1 poliomyelitis)) OR (((chronic NEAR2 epstein Barr virus) OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR ((akureyri OR iceland OR tapanui OR royal free OR royal free hospital) NEAR1 disease*) OR ((yuppie OR yuppy OR tapanui) NEAR1 flu) OR MAINSUBJECT.EXACT.EXPLODE("Chronic Fatigue

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	Syndrome"))) AND (stype.exact("Scholarly Journals") AND la.exact("ENG") AND po.exact("Human") NOT (me.exact("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Clinical Trial" OR "Qualitative Study" OR "Prospective Study" OR "Followup Study" OR "Literature Review" OR "Retrospective Study" OR "Systematic Review" OR "Meta Analysis") AND po.exact("Human"))

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))) OR advanced_abstract_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic

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	epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))))

B.2 Health economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to ME/CFS population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018), with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 2: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 June 2020	Exclusions Health economics studies
Embase	2014 –30 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

1.	Fatigue Syndrome, Chronic/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15

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17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	Economics/
38.	Value of life/
39.	exp "Costs and Cost Analysis"/
40.	exp Economics, Hospital/
41.	exp Economics, Medical/
42.	Economics, Nursing/
43.	Economics, Pharmaceutical/
44.	exp "Fees and Charges"/
45.	exp Budgets/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/37-52
54.	36 and 53

Embase (Ovid) search terms

1.	chronic fatigue syndrome/
2.	chronic* fatigue*.ti,ab.
3.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.

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4.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
5.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
6.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
7.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
8.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
9.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
10.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
11.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
12.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
13.	xenotropic murine leukemia virus-related virus.ti,ab.
14.	effort syndrome*.ti,ab.
15.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	limit 33 to English language
35.	health economics/
36.	exp economic evaluation/
37.	exp health care cost/
38.	exp fee/
39.	budget/
40.	funding/
41.	budget*.ti,ab.
42.	cost*.ti.

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43.	(economic* or pharmaco?economic*).ti.
44.	(price* or pricing*).ti,ab.
45.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
46.	(financ* or fee or fees).ti,ab.
47.	(value adj2 (money or monetary)).ti,ab.
48.	or/35-47
49.	34 and 48

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Fatigue Syndrome, Chronic
#2.	(chronic fatigue or fatigue syndrome*)
#3.	((myalgic adj (encephalomyelitis or encephalopathy)))
#4.	(((ME adj CFS) or (CFS adj ME)))
#5.	(post viral fatigue or post viral syndrome* or viral fatigue syndrome* or PVFS)
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(neurasthenic neuroses or epidemic neuromyasthenia or post infectious encephalomyelitis or neurataxia or neuroasthenia)
#8.	(((atypical or simulating or resembling) adj poliomyelitis))
#9.	(chronic epstein Barr virus or chronic mononucleosis)
#10.	(xenotropic murine leukemia virus-related virus)
#11.	(((chronic fatigue and immune dysfunction syndrome*) or cfids or chronic fatigue-fibromyalgia syndrome* or chronic fatigue disorder* or Systemic Exertion Intolerance Disease or SEID or effort syndrome or post infectious fatigue))
#12.	((((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)))
#13.	#7 OR #8 OR #9 OR #10 OR #11 OR #12
#14.	#6 or #13

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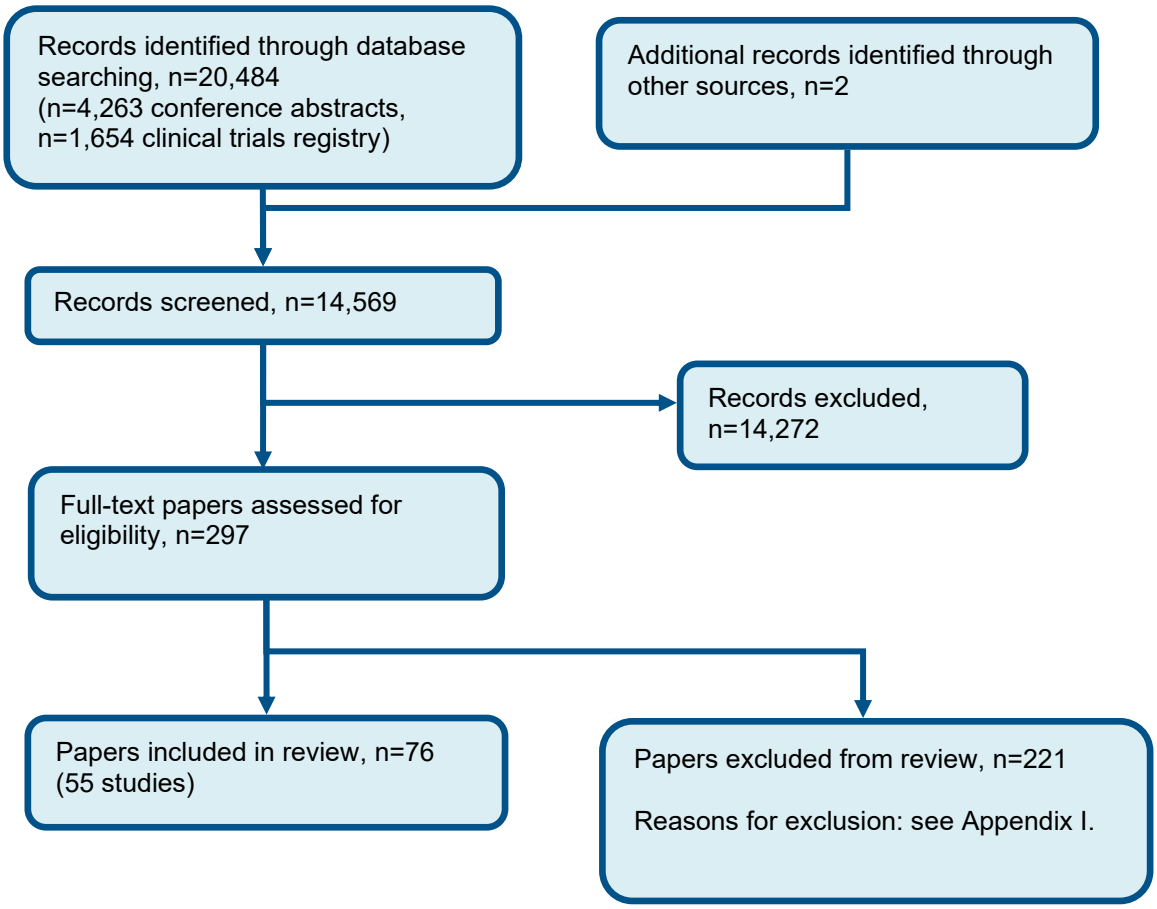
Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of non-pharmacological interventions



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Appendix D Effectiveness evidence

Study	Al-Haggar 2006[14]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=159)
Countries and setting	Conducted in Egypt; Setting: specifically designed CFS clinic run by three well-trained paediatric psychotherapists
Line of therapy	Unclear
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosed according to Fukuda 1994 criteria; evaluation included detailed history taking, clinical examination and routine laboratory investigations
Stratum	Children and young people; severity mixed or unclear: age range 10-14 years, meeting Fukuda 1994 criteria (no further detail on severity)
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Screened positive for chronic fatigue using a questionnaire (The American Academy of Family Physician 1994-2005); detailed history taking, thorough clinical examination and routine laboratory investigations to rule out organic disease; >10 years old; complained of severe fatigue symptoms for >6 months; functional impairment of CIS >40%
Exclusion criteria	Exclusionary criteria of Fukuda; any unexplained physical or laboratory finding must have been resolved before further classification

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Recruitment/selection of patients	Recruited from health records and attendance profiles of students in Egyptian schools of Eastern Province, Saudi Arabia and referral by family doctors, general practitioners and physicians
Age, gender and ethnicity	Age - Mean (SD): intervention group 13.1 (3.2) years; control group 11.9 (2.4) years. Gender (M: F): 25/67. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=81) Intervention 1: Psychological and behavioural interventions - CBT. CBT + Biofeedback: 40-60 sessions once or twice a week then tapered gradually depending on fatigue severity. Sessions included patients and their families. Contact maintained between families and psychotherapists by phone and email to answer queries. Patients were trained to improve their health using signals from their own bodies; biofeedback machines (most commonly muscle monitors and freeze framer for treatment of muscle aches and headache) gave information about internal body functions to direct the progress of CBT. Patients trained to perform relaxation exercises, to identify circumstances that trigger symptoms, to avoid or cope with these stressful events, to change habits and in self-control. Treatment protocols adopted according to activity pattern - active patients who had periods of activity and rest were advised to limit activity and build up gradually, passive patients who spent most of the time at home were assured that activity wouldn't aggravate their symptoms and advised to undergo gradual building up by performing recreational exercises usually in the form of variable non-exhausting walks. Duration 18 months. Concurrent medication/care: Psychotherapists were responsible for arrangement and formulation of all types of therapy; sometimes they consult family doctors for medical treatment of isolated systemic symptoms. No psychotherapeutic drugs were used. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (specifically designed CFS clinic; CBT focused on CFS). (n=78) Intervention 2: usual care - standard medical care. Conservative and symptomatic treatment. Duration 18 months. Concurrent medication/care: Psychotherapists were responsible for arrangement and formulation of all types of therapy; sometimes they consult family doctors for medical treatment of isolated systemic symptoms. No psychotherapeutic drugs were used. Indirectness: No indirectness; Indirectness

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	comment: NA Further details: 1. type of intervention: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus STANDARD MEDICAL CARE Protocol outcome 1: Fatigue at longest follow up available - Actual outcome for children; severity mixed or unclear: Fatigue Assessment Scale % at 18 months; Group 1: mean 32.2 percentage points (SD 3.8); n=50, Group 2: mean 46.5 percentage points (SD 14.2); n=42; Fatigue Assessment Scale 0-100 Top=High is poor outcome; Comments: Baseline values: intervention 54.8 (3.6), control 51.9 (4.3) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no statistically significant baseline differences in demographics or outcome measures; Group 1 Number missing: 31, Reason: lost to follow up due to non-compliance, travels, school examinations and other undetermined factors; Group 2 Number missing: 36, Reason: lost to follow up due to non-compliance, travels, school examinations and other undetermined factors; 4 excluded from analysis due to switching Protocol outcome 2: Return to school or work at longest follow up available - Actual outcome for children; severity mixed or unclear: School attendance (hours/month) at 18 months; Group 1: mean 92.8 hours (SD 18.4); n=50, Group 2: mean 66.6 hours (SD 22.8); n=42; Comments: Baseline values: intervention 64.4 (13.2), control 64.8 (14.5) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no statistically significant baseline differences in demographics or outcome measures; Group 1 Number missing: 31, Reason: lost to follow up due to non-compliance, travels, school examinations and other undetermined factors; Group 2 Number missing: 36, Reason: lost to follow up due to non-compliance, travels, school examinations and other undetermined factors; 4 excluded from analysis due to switching	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	Broadbent 2016[93] (Broadbent 2013[95], Broadbent 2017[94])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Australia; Setting: primary care
Line of therapy	Unclear
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis from participant's medical practitioner, according to the CDC 1994 criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of 'CFS' from the participant's medical practitioner, according to the CDC 1994 criteria, an age range of 18 to 65 years, the ability to communicate in English, and informed consent.
Exclusion criteria	Diagnosed cardiorespiratory, endocrine and metabolic conditions, current musculoskeletal injury that would make exercise participation hazardous;
Recruitment/selection of patients	Patients were recruited from the local community through advertisements at the Southern Cross University campus and Health Clinic, local medical clinics and hospitals, local newspapers, television and radio media.
Age, gender and ethnicity	Age - Mean (SD): 50.9 (10). Gender (M:F): 7/17. Ethnicity: not specified
Further population details	-

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Extra comments	Mean time since diagnosis (SD) was 2.9 (2.6) years; pre intervention self-reported fatigue severity scores ranged between 15.8% (very low) and 100% (severe)
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=8) Intervention 1: Exercise interventions - GET. The 12-week program consisted of GE using a spin cycle ergometer. The exercise sessions were conducted at the Southern Cross University fitness facility, three times per week. All sessions were supervised by an accredited exercise physiologist and postgraduate clinical exercise physiology students. The workloads were determined from the baseline VO2 peak cycle test for each participant. Each exercise session consistent of a 5-min gentle warm-up of unloaded cycling, initially followed by a 10- to 15-min block of GE (load equivalent to 50% VO2peak, RPE 3). Recommended cadence was between 50 and 70 rpm. Exercise sessions were progressed by increasing the duration of the session only as tolerated for each participant. The workload was not increased until participants had achieved three consecutive exercise sessions of 30 min in total with no increase in symptoms, and the increase was 10% of the current workload. If participants reported any increase in fatigue or other symptoms during post-exercise, the exercise intensity was reduced until participants felt able to manage progression. Duration 12 weeks. Concurrent medication/care: Each CFS participant completed a pre- and post-intervention incremental test on a cycle ergometer. The pre intervention test was to determine each participant's peak exercise heart rate (HR), VO2, RER, RPE and power as a basis of their exercise session intensities. Participants completed a three minute warm up of unloaded cycling with the workload then increasing to 10 W/min until volitional exhaustion. Indirectness: No indirectness Further details: 1. type of intervention: Not reported/Unclear: All sessions were supervised by an accredited exercise physiologist and postgraduate clinical exercise physiology students. (n=8) Intervention 2: Exercise interventions - GET. The 12-week program consisted of IE using a spin cycle ergometer. The exercise sessions were conducted at the Southern Cross University fitness facility, three times per week. All sessions were supervised by an accredited exercise physiologist and postgraduate clinical exercise physiology students. The workloads were determined from the baseline VO2 peak cycle test for each participant. Each exercise session consistent of a 5-min gentle warm-up of unloaded cycling, initially followed by a 10- to 15-min block of IE of 1 minute of moderate intensity cycling (60% VO2peak, RPE 4-5) alternated with 1 minute of unloaded or very low-intensity cycling (30% VO2peak, RPE 1-2). Recommended cadence was between 50 and 70 rpm. Exercise sessions were progressed by increasing the duration of the

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	session only as tolerated for each participant. The workload was not increased until participants had achieved three consecutive exercise sessions of 30 min in total with no increase in symptoms, and the increase was 10% of the current workload. If participants reported any increase in fatigue or other symptoms during post-exercise, the exercise intensity was reduced until participants felt able to manage progression. Duration 12 weeks. Concurrent medication/care: Each CFS participant completed a pre- and post-intervention incremental test on a cycle ergometer. The pre intervention test was to determine each participant's peak exercise heart rate (HR), VO2, RER, RPE and power as a basis of their exercise session intensities. Participants completed a three minute warm up of unloaded cycling with the workload then increasing to 10 W/min until volitional exhaustion. Indirectness: No indirectness Further details: 1. type of intervention: Not reported/Unclear: All sessions were supervised by an accredited exercise physiologist and postgraduate clinical exercise physiology students. (n=8) Intervention 3: usual care - standard medical care. Participants were asked to follow the advice of their medical practitioner (rest and maintaining activity for daily activities) and not engage in any other physical activity during the study. Duration 12 weeks. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: not applicable
Funding	Other (the O.J. and J.R. Wicking Trust and Mason Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GRADED EXERCISE (GE) versus INTERMITTENT EXERCISE (IE) Protocol outcome 1: Exercise performance measure at longest follow up available - Actual outcome for Severity and age mixed or unclear: VO2peak (mL/kg/min) at 12 weeks post intervention; Group 1: mean 23.2 (SD 4); n=8, Group 2: mean 24.5 (SD 7); n=8; Comments: VO2 peak refers to Aerobic capacity Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in fatigue severity scores that could potentially be confounding; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified - Actual outcome for Severity and age mixed or unclear: Peak power (W) at 12 weeks post intervention; Group 1: mean 102 (SD 15); n=8, Group 2: mean	

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108.8 (SD 12); n=8
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline resting peak power (W) scores (mean (SD)) are: 96.2 (11) vs 100 (14) for GE and IE groups respectively and there are additional baseline differences in fatigue severity scores that could potentially be confounding; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: V Epeak (L/min) at 12 weeks post intervention; Group 1: mean 52.7 (SD 14); n=8, Group 2: mean 58.4 (SD 11); n=8; Comments: not defined but probably refers to peak expiratory flow i.e. person's maximum speed of expiration.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline resting HR scores (mean (SD)) are: 44.5 (11) vs 48.5 (13) for GE and IE group respectively and there are additional baseline differences in fatigue severity scores that could potentially be confounding; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Elapsed test time (min) at 12 weeks post intervention; Group 1: mean 11.9 (SD 2); n=8, Group 2: mean 12.9 (SD 3); n=8
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in fatigue severity scores that could potentially be confounding; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Rated perceived exertion- RPE (0-10) at 12 weeks post intervention; Group 1: mean 6.9 (SD 1); n=8, Group 2: mean 7.1 (SD 1); n=8; Comments: pre-exercise in IE group 7.1 (SD 1), GET group 6.7 (SD 1)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in fatigue severity scores that could potentially be confounding; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GRADED EXERCISE (GE) versus STANDARD CARE

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Protocol outcome 1: Exercise performance measure at longest follow up available
- Actual outcome for Severity and age mixed or unclear: VO2peak (mL/kg/min) at 12 weeks post intervention; Group 1: mean 23.2 (SD 4); n=8, Group 2: mean 19.7 (SD 8); n=8
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in mean (SD) Body mass (kg): 69 (15) vs 78.7. Weight is related to various factors including age, height and muscle mass, but considering that mean age and height are similar between the groups, baseline differences in body mass could potentially be confounding; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Peak power (W) at 12 weeks post intervention; Group 1: mean 102.5 (SD 15); n=8, Group 2: mean 94.2 (SD 39); n=8
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in Body mass (kg) potentially confounding since mean age and height were similar; baseline peak power scores: 96.2 (11) vs 92.7 (33) for GE vs UC groups respectively; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: V Epeak (L/min) at 12 weeks post intervention; Group 1: mean 52.7 (SD 14); n=8, Group 2: mean 44.7 (SD 14); n=8; Comments: not defined but probably refers to peak expiratory flow i.e. person's maximum speed of expiration.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in mean (SD) Body mass (kg): 69 (15) vs 78.7 (22). Weight is related to various factors including age, height and muscle mass, but considering that mean age and height are similar between the groups, baseline differences in body mass could potentially be confounding. ; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Elapsed test time (min) at 12 weeks post intervention; Group 1: mean 11.9 (SD 2); n=8, Group 2: mean 11.3 (SD 4); n=8
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in baseline body mass (kg) which

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due to age and height being similar, could potentially be confounding; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Rated perceived exertion (RPE) at 12 weeks post intervention; Group 1: mean 6.9 (SD 1); n=8, Group 2: mean 6.6 (SD 1); n=8; Comments: pre-exercise in GET group 6.7 (SD 1), UC group 6.6 (SD 1)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in mean (SD) Body mass (kg): 69 (15) vs 78.7 (22). Weight is related to various factors including age, height and muscle mass, but considering that mean age and height are similar between the groups, baseline differences in body mass could potentially be confounding. ; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTERMITTENT EXERCISE (IE) versus STANDARD CARE

Protocol outcome 1: Exercise performance measure at longest follow up available
- Actual outcome for Severity and age mixed or unclear: VO2peak (ml/kg/min) at 12 weeks post intervention; Group 1: mean 24.5 (SD 7); n=8, Group 2: mean 19.7 (SD 8); n=8
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in fatigue severity scores (related to implications of fatigue on daily living): 71.6% (23.7%) vs 85.1% (10.8%) could indicate different disease severity between groups; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Peak power (W) at 12 weeks post intervention; Group 1: mean 108.8 (SD 12); n=8, Group 2: mean 94.2 (SD 39); n=8
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline outcome scores (mean (SD)) are: 100 (14) vs 92.7 (33) for IE and UC group; baseline differences in fatigue severity scores (related to implications of fatigue on daily living): 71.6% (23.7%) vs 85.1% (10.8%) could indicate different disease severity between groups; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

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- Actual outcome for Severity and age mixed or unclear: V Epeak (L/min) at 12 weeks post intervention; Group 1: mean 58.4 (SD 11); n=8, Group 2: mean 44.7 (SD 14); n=8
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline outcome scores (mean (SD)) are: 43.4(15) vs 48.5 (13) for IE and UC group; baseline differences in fatigue severity scores (related to implications of fatigue on daily living): 71.6% (23.7%) vs 85.1% (10.8%) could indicate different disease severity between groups; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Elapsed test time (min) at 12 weeks post intervention; Group 1: mean 12.9 (SD 3); n=8, Group 2: mean 11.3 (SD 4); n=8
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in fatigue severity scores (related to implications of fatigue on daily living): 71.6% (23.7%) vs 85.1% (10.8%) could indicate different disease severity between groups; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

- Actual outcome for Severity and age mixed or unclear: Rated perceived exertion (RPE) at 12 weeks post intervention; Group 1: mean 7.1 (SD 1); n=8, Group 2: mean 6.6 (SD 1); n=8 Comments: pre-exercise in UC group 6.6 (SD 1), IE group 7.1 (SD 1)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in fatigue severity scores (related to implications of fatigue on daily living): 71.6% (23.7%) vs 85.1% (10.8%) could indicate different disease severity between groups; Blinding details: It was not possible to blind participants and caregivers due to the nature of the interventions but this is unlikely to have influences the outcome; Group 1 Number missing: unclear, Reason: not specified; Group 2 Number missing: unclear, Reason: not specified

Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; activity levels at longest follow up available; Return to school or work at longest follow up available

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Study	Brouwers 2002[99]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in Netherlands; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks (2 weeks for baseline measurements + 10 week intervention)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical diagnosis of CFS according to 1994 CDC criteria
Stratum	adults; severity mixed or unclear: minimum age for participation was 18 years; minimum fatigue severity scores for participation were 40 on the subscale subjective fatigue of the Checklist Individual Strength and disability scores were 750 on the total Sickness Impact Profile disability scores
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Had to fulfill the 1994 CDC criteria for chronic fatigue syndrome; high fatigue severity scores (CIS-fatigue ≥40) and high disability scores (SIP8-total ≥750); age ≥18 years
Exclusion criteria	Pregnant or lactating women; patients with intolerance for lactose; patients who used experimental medication; during the trial, patients were not allowed to take vitamins and minerals (other than the trial supplements) and the use of vitamins and other supplements had to be discontinued 4 weeks prior to entry into the study

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Recruitment/selection of patients	All patients were recruited from a database of the department of General Internal Medicine of a single University Medical Center. The database consisted of clinically diagnosed CFS patients who at the time of diagnosis indicated that they were interested in participating in research projects.
Age, gender and ethnicity	Age - Mean (SD): 39.3 (10.3) years. Gender (M:F): 16/37. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=27) Intervention 1: dietary supplementation. Nutritional supplement (125ml) containing several vitamins, minerals and coenzymes, specifically developed to have a high antioxidative capacity, twice daily. Duration 10 weeks. Concurrent medication/care: During the trial, patients were not allowed to take vitamins and minerals (other than the trial supplements). Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=26) Intervention 2: placebo or sham - placebo. Identical appearing placebo (125ml) twice daily. Duration 10 weeks. Concurrent medication/care: During the trial, patients were not allowed to take vitamins and minerals (other than the trial supplements). Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Equipment / drugs provided by industry (Numico Research BV (includes Nutricia, Milupa, Cow&Gate, SHS, GNC, Unicity Network, Rexall Sundown, Biodermal and Galenco))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYNUTRIENT SUPPLEMENT versus PLACEBO/SHAM Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: Self-reported improvement in severity of complaints (number reporting completely recovered) at 12 weeks; Group 1: 0/27, Group 2: 0/26 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear	

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- Actual outcome for adults; severity mixed or unclear: Self-reported improvement in severity of complaints (number reporting improved) at 12 weeks; Group 1: 5/27, Group 2: 4/26; Comments: numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Self-reported improvement in severity of complaints (number reporting similar) at 12 weeks; Group 1: 21/27, Group 2: 18/26; Comments: numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Self-reported improvement in severity of complaints (number reporting worse) at 12 weeks; Group 1: 1/27, Group 2: 0/26; Comments: numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile-8 at 12 weeks; Group 1: mean 1650 (SD 543); n=27, Group 2: mean 1710 (SD 644); n=26; Sickness Impact Profile-8 not reported Top=High is poor outcome; Comments: Baseline values: poly nutrient supplement 1911 (666), placebo 1811 (683)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual Strength (fatigue sub scale) at 12 weeks; Group 1: mean 48.6 (SD 7.4); n=27, Group 2: mean 48.2 (SD 7.6); n=26; Checklist Individual Strength fatigue sub scale 8-56 Top=High is poor outcome; Comments: Baseline values: supplement 51.4 (4.2), placebo 51.3 (3.6)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear

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Protocol outcome 4: Adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: nausea at 12 weeks; Group 1: 3/27, Group 2: 0/26 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear Protocol outcome 5: Activity levels at longest follow up available - Actual outcome for adults; severity mixed or unclear: Actometer score (average score over 2 weeks) at 12 weeks; Group 1: mean 57.2 accelerations (SD 14.6); n=27, Group 2: mean 65.6 accelerations (SD 22.4); n=26; activity level 0-300 Top=High is good outcome; Comments: Baseline values: supplement 62.9 (17.9), placebo 65.8 (19.4) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 0, Reason: unclear	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	Castro-Marrero 2016[126] (Castro-Marrero 2015[124])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in Spain; Setting: single tertiary referral center
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 CDC case criteria
Stratum	adults; severity mixed or unclear: age between 18 and 65 years with a confirmed diagnosis of CFS according to 1994 CDC case criteria
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Female sex, age between 18 and 65 years with a confirmed diagnosis of CFS according to 1994 CDC case criteria; all participants had a resting radial pulse rate between 50 and 100 bpm, systolic blood pressure between 100 and 140 mmHg and diastolic blood pressure between 50 and 90 Hg
Exclusion criteria	Contraindication of an ergometer exercise test, participation in other trials in the 30 days prior to inclusion, intake of any drug or banned substances (statins, dietary supplements, anti-hypertension or beta-blocker drugs), pregnancy or breast-feeding, secondary hypertension, hepatobiliary tract disease that might alter CoQ10 bio availability, cardiovascular or pulmonary disorder (unstable angina pectoris, heart failure, life-threatening arrhythmia) that might interfere with maximal exercise testing, and inability to communicate and comply with all study requirements.

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Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 49.2 ± 7.8 years. Gender (M:F): 0/80. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=40) Intervention 1: dietary supplementation - co-enzyme Q10. CoQ10 plus nicotinamide adenine dinucleotide in enteric-coated tablets (50 mg of CoQ10 and 5 mg of NADH) and excipients (20 mg of phosphatidylserine and 40 mg of vitamin C), two tablets twice daily. Duration 8 weeks. Concurrent medication/care: Standard therapy. Participants were instructed to avoid taking any additional supplements containing CoQ10, NADH, phosphatidylserine and vitamin C during the study. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=40) Intervention 2: placebo or sham - placebo/sham. Identical appearing enteric coated tablets without active ingredients and containing only excipients, two tablets twice daily. Duration 8 weeks. Concurrent medication/care: Standard therapy. Participants were instructed to avoid taking any additional supplements containing CoQ10, NADH, phosphatidylserine and vitamin C during the study. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Principal author funded by industry (lead author received financial support from Vitae Natural Nutrition Co., S.L, who also supplied the study tablets)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CO-ENZYME Q10 versus PLACEBO/SHAM

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue index scale total score
at 8 weeks; Group 1: mean 124.4 (SD 23.4); n=39, Group 2: mean 132.3 (SD 20.7); n=34; Fatigue index scale 0-160 Top=High is poor outcome; Comments: Baseline values: supplement group 131.9 (18.9), placebo group 136 (16)

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Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3)

Protocol outcome 2: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: McGill pain questionnaire - sensory sub scale
at 8 weeks; Group 1: mean 21.8 (SD 6); n=39, Group 2: mean 17.7 (SD 7.4); n=34; McGill pain questionnaire sensory sub scale 0-33 Top=High is poor outcome; Comments: Baseline values: supplement group 20.2 (4.7), placebo 22.1 (5.6)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3)
- Actual outcome for adults; severity mixed or unclear: McGill pain questionnaire - affective sub scale
at 8 weeks; Group 1: mean 8.9 (SD 3.1); n=39, Group 2: mean 6.8 (SD 3.6); n=34; McGill pain questionnaire affective sub scale 0-12 Top=High is poor outcome; Comments: Baseline values: supplement group 8.5 (2.6), placebo group 8.8 (3.1)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3)

Protocol outcome 3: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Global Pittsburgh sleep quality index
at 8 weeks; Group 1: mean 15.8 (SD 4.5); n=39, Group 2: mean 14.9 (SD 2.7); n=34; Pittsburgh sleep quality index 0-21 Top=High is poor outcome; Comments: Baseline values: supplement group 14.6 (3.4), placebo group 15.9 (3.2)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3)

Protocol outcome 4: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: adverse events
at 8 weeks; Group 1: 0/40, Group 2: 3/40; Comments: adverse events: abdominal pain and discomfort (n=2), orthostatic intolerance (n=1), moderate and considered unrelated to placebo
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason:

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Protocol outcome 5: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Workload (km/h) during an incremental cycle ergometer stress test at 8 weeks; Group 1: mean 93.2 km/hr (SD 21.4); n=40, Group 2: mean 88.8 km/hr (SD 19.7); n=40; workload NA Top=High is good outcome; Comments: Baseline values: supplement group 92.8 (20.7), placebo group 91.9 (21.7) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3) -Actual outcome for adults; severity mixed or unclear: VO2 max during an incremental cycle ergometer stress test at 8 weeks; Group 1: mean 18.6 (SD 3.2); n=40, Group 2: mean 18.6 (SD 3.8); n-40; VO2 max; Comments: Baseline values: supplement group 19.4 (4.3), placebo group 19.7 (3.3) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3) - Actual outcome for adults; severity mixed or unclear: Perceived exertion on an incremental cycle ergometer stress test measured by the Borg scale at 8 weeks; Group 1: mean 0.25 (SD 1.35); n=40, Group 2: mean 0.12 (SD 1.63); n=40; Borg scale 6-20 Top=High is poor outcome; Comments: Baseline values not reported. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up; Group 2 Number missing: 6, Reason: refusal to participate (n=2), loss of a cycling ergometer test (n=1), adverse events (n=3)	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available

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Study	Collinge 1998[183]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in USA; Setting: Community
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Current diagnosis of CFS by a physician (interval of at least 12 months since diagnosis), meeting the CDC criteria (Fukuda 1994) and no other major medical conditions. These factors were independently confirmed by the subject's physician.
Stratum	Adults; severity mixed or unclear: An estimated global functioning level of 75% or less - no further info on severity. Age range of included participants 27-61 years.
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	A current diagnosis of CFS by a physician according to CDC criteria; an interval of at least 12 months since diagnosis; an estimated global functioning level of 75% or less; willingness to be randomly assigned to either the control or experimental group; willingness to comply with a regime of self-help practices if assigned to the intervention group
Exclusion criteria	Other major medical conditions such as cancer, AIDS, MS, etc; current or recent participation in behavioural or mind/body medicine treatment programs, individually or group; current regular use of behavioural or mind/body self-healing practices
Recruitment/selection of patients	A call for subjects was sent by mail to physicians recognized as having expertise in CFS, who announced the study through postings in their waiting rooms and their individual contacts with patients

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Age, gender and ethnicity	Age - Range: 27-61 years. Gender (M:F): 10/50. Ethnicity: Caucasian majority (92%)
Further population details	-
Extra comments	Months since diagnosis, mean (SD): 57 (28.1) Mean age: 44.2 (reported SD 70 which is likely a typo).
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=37) Intervention 1: Psychological and behavioural interventions – mindfulness and medical qigong combined intervention. 9 week group behavioural medicine program, 2 hours per week. Each session consisted of instruction and guided practice of two techniques: mindfulness meditation and medical qigong. Mindfulness component (30 minutes) - based on traditional Buddhist practice involving sitting still with eyes closed and focusing on one's attention on the breath. Medical qigong (30 minutes) - a set of exercises performed sitting or standing, based on traditional Chinese system of self-healing exercises that involve breathing, self-massage, movement, imagery, and circulation of vital energy. Participants were also asked to practice one or both techniques for at least 30 minutes per day at home. To support home practice each subject had a partner (another participant) who they would phone on alternate days to offer encouragement. Subjects used daily log sheets to record their at home practice. Participants were also encouraged to share their experience of the past week in group discussion, with a focus on integrating self-healing practices into daily life. Duration 9 weeks. Concurrent medication/care: Usual medical care (not further defined). Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (No info on who delivered intervention). Comments: Combined intervention involving both mindfulness meditation and medical qigong (n=33) Intervention 2: usual care - standard medical care. Continued usual care (not further defined). Duration 9 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Other (Charitable foundation (Stupski Family Fund))

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINDFULNESS MEDITATION + MEDICAL QIGONG versus USUAL MEDICAL CARE Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: Improvement in SF36 health transition score at 12 months; Group 1: 13/28, Group 2: 19/32; Comments: SF-36 12-month health transition measure: 'Compared to one year ago how would you rate your health in general now?' Scale 1-5; 1=much better, 2=somewhat better, 3=about the same, 4=somewhat worse, 5=much worse. Participants reporting improvement – defined as scores of 1 or 2. Baseline SF-36 health transition score (over the year prior to study) - mean (SD) - 2.77 (1.13) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details only reported for study population as a whole, so unable to compare groups; Blinding details: subjective patient assessed outcome; Group 1 Number missing: 9, Reason: n=8 dropped out due to logistical issues such as transport or time conflicts; n=1 removed from study for disruptive behaviour; Group 2 Number missing: 1, Reason: n=1 declined to complete data collection	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	Chalder 2010[138] (Lloyd 2012[457])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=63)
Countries and setting	Conducted in United Kingdom; Setting: unclear
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: fulfilled either the Oxford or CDC (Centers for Disease Control and Prevention) criteria for CFS. All were investigated by a paediatrician, prior to referral, to exclude alternative causes for their fatigue. A clinical assessment involving all members of the family took place to establish whether the adolescent had 'CFS/ME' according to either the CDC or Oxford criteria.
Stratum	Children and young people; severity mixed or unclear: between the ages of 11 and 18 years; fulfilling either the Oxford or CDC criteria for CFS - no further detail on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Fulfilled either the Oxford or CDC (Centers for Disease Control and Prevention) criteria for CFS
Exclusion criteria	Major depression, somatization disorder, conversion disorder, history of self-harm or an identifiable disease that could have contributed to illness, made on the basis of a clinical assessment by an experienced therapist. Patients taking anti-depressants were not excluded. However, they had to be on a stable dose for 3 months before entering the trial.
Recruitment/selection of patients	Referred to King's College Hospital London by their general practitioner or consultant paediatrician for an assessment of their CFS screened for inclusion

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Age, gender and ethnicity	Age - Median (IQR): 15 (14-17) years. Gender (M:F): 20/43. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC/Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=32) Intervention 1: Psychological and behavioural interventions - CBT. 13 x 1-h sessions of CBT every 2 weeks. Treatment protocol adapted from that used in a trial of CBT for CFS in adults (Deale et al. 1997), taking into account the specific needs of this age group. Particular emphasis placed on building a rapport with all members of the family and establishing a collaborative relationship. Involved encouraging the participant to achieve a balance between activity and rest; gradually increasing activities including home, social and school life; establishing a sleep routine; addressing beliefs such as fear regarding the relative benefits of activity and/or exercise, high self-expectations and all-or-nothing thinking; encouraging individuals within the family to express their own views about the illness and agreeing a way forward and paying attention to relapse prevention. The parent providing the majority of the care was supported as the adolescents became more independent. Homework assignments were negotiated with participants at each session. A treatment guide, Self Help for Chronic Fatigue Syndrome: A Guide for Young People (Chalder & Husain, 2002), was given to the family. Therapists sought to maintain neutrality and acted as brokers in the not infrequent adolescent/parent disputes. Delivered by two trained and experienced cognitive behavioural psychotherapists. Duration 6 months. Concurrent medication/care: Close liaison with relevant school teachers and home tutors was initiated from the start of treatment and maintained throughout. Key issues for discussion were: endorsement of the reality of the condition, negotiating a graded return to school and for some reducing the number of subjects taken. In some cases, repeat years were negotiated. Anxieties about reintegrating with peer groups were addressed and some adolescents were supported in changing academic institutions altogether. In both groups the entire family was invited to the first session and the mother accompanied the child to every subsequent session. Other members of the family attended when they could. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (CBT designed for CFS but unclear whether therapists were specialised/experienced in CFS). (n=31) Intervention 2: self-management - pacing. Psycho-education: 4 sessions over a 6-month period. Content similar to CBT, but mode of delivery was didactic. Involved discussion, information giving and

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	problem solving but specific homework assignments and cognitive restructuring not included. Families were not given a manual. Therapists ensured adherence to protocol by working from a checklist that included the following. (a) Gave the message that untreated CFS in adolescents has a good prognosis. (b) Presented a model of CFS that distinguished predisposing, precipitating and maintaining factors. (c) Introduced the concept of symptom management – that the way we manage our physical symptoms can make a difference to the outcome. Physical illness analogies such as heart disease were used to increase likelihood of engagement. (d) Gave advice on pacing and consistency of activity and rest, in order to break the vicious circle of symptom lead behaviour. (e) Gave advice on sleep management. (f) Conveyed the message that hurt does not equal harm – increased symptoms do not mean more pathology. (g) Advised clients to gradually build up activity over a period of months. Duration 6 months. Concurrent medication/care: Close liaison with relevant school teachers and home tutors was initiated from the start of treatment and maintained throughout. Key issues for discussion were: endorsement of the reality of the condition, negotiating a graded return to school and for some reducing the number of subjects taken. In some cases, repeat years were negotiated. Anxieties about reintegrating with peer groups were addressed and some adolescents were supported in changing academic institutions altogether. In both groups the entire family was invited to the first session and the mother accompanied the child to every subsequent session. Other members of the family attended when they could. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (designed for CFS but unclear whether therapists were specialised/experienced in CFS).
Funding	Academic or government funding (NHS Executive London Region Office)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FAMILY FOCUSED CBT versus PSYCHO-EDUCATION Protocol outcome 1: General symptom scales longest follow up available - Actual outcome for Severity and age mixed or unclear: Self-reported global improvement - much better or very much better at 24 months; Group 1: 19/24, Group 2: 18/20; Comments: numbers calculated from percentages reported in the follow up paper; participants rated degree of improvement in fatigue and disability on a nine-point scale from 'much better' to 'much worse'. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 8, Reason: unclear; Group 2 Number missing: 11, Reason: unclear	

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- Actual outcome for Severity and age mixed or unclear: Strengths and Difficulties Questionnaire at 24 months; Group 1: mean 9.63 (SD 4.28); n=24, Group 2: mean 13.61 (SD 4.24); n=20; Strengths and Difficulties Questionnaire 0-40 Top=High is poor outcome; Comments: Baseline values: CBT 15.16 (5.61), psycho-education 13.52 (4.64)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 8, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Chalder Fatigue Scale at 24 months; Group 1: mean 10.4 (SD 5.7); n=24, Group 2: mean 12.15 (SD 4.79); n=20; Chalder Fatigue Scale 0-33 Top=High is poor outcome; Comments: Baseline values: CBT 22.26 (5.71), psycho-education 29.43 (4.66)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 8, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for Severity and age mixed or unclear: SF36 physical functioning at 24 months; Group 1: mean 76.79 (SD 29.81); n=24, Group 2: mean 71.2 (SD 27.99); n=20; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 51.25 (26.34), psycho-education 41.67 (24.34)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 8, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 4: Adverse events at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Serious adverse events at 6 months; Group 1: 1/32, Group 2: 0/31; Comments: one participant who received family-focused CBT was admitted to hospital with depression after discharge from treatment, during the follow-up phase
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

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Protocol outcome 5: Return to school or work at longest follow up available - Actual outcome for Severity and age mixed or unclear: % school attendance at 6 months; Group 1: mean 73.4 (SD 34); n=32, Group 2: mean 64.9 (SD 45.6); n=27; % school attendance over 2 weeks 0-100 Top=High is good outcome; Comments: Baseline values (median, IQR): CBT 23 (0-55), psycho-education 17 (0-50)% Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 4, Reason: unclear - Actual outcome for Severity and age mixed or unclear: Work and Social Adjustment Scale at 6 months; Group 1: mean 2.5 (SD 1.9); n=29, Group 2: mean 3.3 (SD 2.2); n=27; Work and social adjustment scale 0-40 Top=High is poor outcome; Comments: Baseline values: CBT 4.7 (1.5), psycho-education 5.4 (1.4) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 4, Reason: unclear - Actual outcome for Severity and age mixed or unclear: Work and Social Adjustment Scale at 24 months; Group 1: median 0.60 (IQR 0.00–2.40); n=24, Group 2: median 1.610 (IQR 0.65–2.95); n=20; Work and social adjustment scale 0-40 Top=High is poor outcome; Comments: Baseline values: CBT 4.7 (1.5), psycho-education 5.4 (1.4) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: physical functioning and school attendance were worse in the psycho-education group whereas the duration of fatigue symptoms was longer in the CBT group; Group 1 Number missing: 8, Reason: Overall, 14 declined to take part and 5 were not contactable.; Group 2 Number missing: 11, Reason: Overall, 14 declined to take part and 5 were not contactable..	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	Deale, 1997 trial: Deale 1997[225] (Deale 2001[228])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in United Kingdom; Setting: Hospital clinic specializing in CFS (participants had been referred to the clinic from primary care physicians and consultants).
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of chronic fatigue syndrome was made according to U.K. (Oxford criteria) (U.S. (Schluederberg/1991 CDC criteria) case definitions; patient received a standardized assessment interview with a consultant psychiatrist experienced in chronic fatigue syndrome (S.W.). A full history was taken.
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	A main complaint of medically unexplained, disabling fatigue of at least 6 months' duration, with impairment of physical and mental activities (Sharpe criteria). Patients taking antidepressant medication or anxiolytics (at a dose no greater than 10 mg/day of diazepam or equivalent) were eligible if the dose was stable for 3 months before entry and during the trial.
Exclusion criteria	Somatization disorder, severe depression (DSM -III-R melancholic subtype), ongoing physical investigations, concurrent new treatment, and inability to attend all treatment sessions.
Recruitment/selection of patients	Consecutive

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Age, gender and ethnicity	Age - Mean (range): 31-38 (mean 34.5). Gender (M:F): 19:41. Ethnicity: unclear
Further population details	-
Extra comments	CBT/relaxation: age 31/38; illness duration 3.4yrs/4.6 years; female 70%/67%; married 27%/33%; social class I or II 67%/63%; disability benefit 53%/67%; current psychiatric diagnosis 37%/40%; past psychiatric diagnosis 30%/13%; on antidepressants 13%/27%; patient attribution of symptoms to physical illness 57%/73%
Indirectness of population	Serious indirectness: 1991 CDC/Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=30) Intervention 1: Psychological and behavioural interventions - CBT. This treatment was collaborative, educative, and negotiated and had a behavioral emphasis. The aim was to show patients that activity could be increased steadily and safely without exacerbating symptoms. Sessions 1 to 3 involved engaging the patients in therapy and offering a detailed treatment rationale. Presenting problems were assessed, and patients kept diaries recording hourly details of activity, rest, and fatigue. At session 4 a schedule of planned, consistent, graded activity and rest was agreed on. The initial targets were modest and small enough to be sustained despite fluctuations in symptoms. Rather than being symptom dependent, activity and rest were divided into small, manageable portions spread across the day (for example, three 5-minute walks daily rather than a 45-minute walk once a week). Patients were encouraged to persevere with their targets and not to reduce them on a bad day or exceed them on a good day. Once a structured schedule was established, activity was gradually increased and rest was reduced, step by step as tolerance developed. Therapist and patient agreed on specific daily targets covering a range of activities (such as walking, reading, visiting friends, or gardening). A sleep routine was established—for example, stopping daytime sleep, rising at a specific time each morning, reducing time in bed, and using stimulus control techniques for insomnia. Cognitive strategies were introduced at session 8 (while the graded activity program continued). Patients recorded any unhelpful or distressing thoughts and, in discussion and as homework, practiced generating alternatives. The unhelpful or distressing thoughts included fears about symptoms and treatment, perfectionism, self- criticism, guilt, and performance expectations. In the final sessions, strategies for dealing with setbacks were rehearsed and patients drew up “action plans” to guide them through the coming months. The importance of maintaining the principles of therapy after discharge was reinforced. Duration 4-6 months. Concurrent medication/care: Each patient received 13 treatment sessions over 4 to 6 months. All

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	patients were seen individually, at weekly or fortnightly intervals. Mean therapist time per patient was 15 hours. Information leaf- lets supplemented each phase of treatment. Each session began with a homework review and ended with agreement on homework tasks, which were recorded in daily diaries. The therapist followed detailed session-by-session treatment manuals devised for both cognitive behaviour therapy and relaxation. The research team met fortnightly to review cases and ensure protocol adherence. Indirectness: No indirectness Further details: 1. type of intervention: Not stated / Unclear (n=30) Intervention 2: Relaxation techniques - relaxation techniques (i.e. Alexander technique). The same session structure was followed in the relaxation group. The first three sessions involved engagement, rationale giving, information gathering, and diary keeping (recording daily events, feelings, fatigue, and muscle tension). No advice about scheduling activity, reducing rest, or altering sleep patterns was given. The relaxation techniques were adapted from applied relaxation training. Progressive muscle relaxation, visualization, and rapid relaxation skills were taught during the 10 treatment sessions and were practiced twice daily as homework. Duration 4-6 months. Concurrent medication/care: Each patient received 13 treatment sessions over 4 to 6 months. All patients were seen individually, at weekly or fortnightly intervals. Mean therapist time per patient was 15 hours. Information leaf- lets supplemented each phase of treatment. Each session began with a homework review and ended with agreement on homework tasks, which were recorded in daily diaries. The therapist followed detailed session-by-session treatment manuals devised for both cognitive behaviour therapy and relaxation. The research team met fortnightly to review cases and ensure protocol adherence. Indirectness: No indirectness Further details: 1. type of intervention: Not stated / Unclear
Funding	Academic or government funding (South East Thames Regional Health Authority LORS)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus RELAXATION TECHNIQUES (IE ALEXANDER TECHNIQUE)

Protocol outcome 1: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Self rating of much better or very much better fatigue at 5 years; Group 1: 17/25, Group 2: 10/28; Comments: Since completing the interventions, 14 CBT and 16 relaxation participants received further treatment: 6 relaxation participants received CBT, other treatments used were antidepressants, counselling, physiotherapy and complementary medicine; comments: Global improvement was rated on a 7-point scale from “very much better” to “very much worse.” Ratings were collapsed into dichotomous categories: “much better” and “very much better”

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versus “a little better,” “unchanged,” “a little worse,” “much worse,” and “very much worse.”
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 5, Reason: 3 refused to participate, 2 untraceable; Group 2 Number missing: 2, Reason: 2 refused to participate

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue problem rating at 6 months; Group 1: mean 3.4 (SD 2.2); n=27, Group 2: mean 5.5 (SD 1.9); n=26; Comments: Similar at baseline - CBT 7 and relaxation 6.3. Slight bias favoured relaxation and so does not assist observed effect. In paper stated that 30 in each group but known that 3 dropped out in CBT group and 4 in relaxation group. Unclear if any imputation performed by study authors so n adjusted to those attending follow up to prevent artificial reduction in SE.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 3, Reason: 1 found CBT ineffective, 1 too ill to attend and 1 improved; Group 2 Number missing: 4, Reason: 1 too ill to attend, 1 no reason and 2 found exercises too tiring

- Actual outcome for adults; severity mixed or unclear: Fatigue questionnaire at 6 months; Group 1: mean 4.1 (SD 4); n=27, Group 2: mean 7.2 (SD 4); n=26; Comments: Similar at baseline - CBT 10.2 and relaxation 9.5. Slight bias favoured relaxation and so does not assist observed effect. In paper stated that 30 in each group but known that 3 dropped out in CBT group and 4 in relaxation group. Unclear if any imputation performed by study authors so n adjusted to those attending follow up to prevent artificial reduction in SE.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 3, Reason: 1 found CBT ineffective, 1 too ill to attend and 1 improved; Group 2 Number missing: 4, Reason: 1 too ill to attend, 1 no reason and 2 found exercises too tiring

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Medical outcomes study short form general health survey physical functioning scale at 6 months; Group 1: mean 71.6 (SD 28); n=27, Group 2: mean 38.4 (SD 26.9); Comments: Similar at baseline – CBT 25.5 (18.9), relaxation 27.8 (27.1). In paper stated that 30 in each group but known that 3 dropped out in CBT group and 4 in relaxation group. Unclear if any imputation performed by study authors so n

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adjusted to those attending follow up to prevent artificial reduction in SE.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 3, Reason: 1 found CBT ineffective, 1 too ill to attend and 1 improved; Group 2 Number missing: 4, Reason: 1 too ill to attend, 1 no reason and 2 found exercises too tiring

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck depression inventory at 6 months; Group 1: mean 10.1 (SD 6.9); n=27, Group 2: mean 12.3 (SD 8.5); n=26; Comments: Similar at baseline - CBT 14.5 and relaxation 14.2. Slight bias favoured relaxation and so does not assist observed effect. In paper stated that 30 in each group but known that 3 dropped out in CBT group and 4 in relaxation group. Unclear if any imputation performed by study authors so n adjusted to those attending follow up to prevent artificial reduction in SE.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 3, Reason: 1 found CBT ineffective, 1 too ill to attend and 1 improved; Group 2 Number missing: 4, Reason: 1 too ill to attend, 1 no reason and 2 found exercises too tiring

- Actual outcome for adults; severity mixed or unclear: General health questionnaire - 12 item at 6 months; Group 1: mean 3.4 (SD 3.7); n=27, Group 2: mean 4.3 (SD 3.9); n=26; Comments: Similar at baseline - CBT 6.2 and relaxation 6.0. Slight bias favoured relaxation and so does not assist observed effect. In paper stated that 30 in each group but known that 3 dropped out in CBT group and 4 in relaxation group. Unclear if any imputation performed by study authors so n adjusted to those attending follow up to prevent artificial reduction in SE.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 3, Reason: 1 found CBT ineffective, 1 too ill to attend and 1 improved; Group 2 Number missing: 4, Reason: 1 too ill to attend, 1 no reason and 2 found exercises too tiring

Protocol outcome 5: Return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and social adjustment scale at 6 months; Group 1: mean 3.3 (SD 2.2); n=27, Group 2: mean 5.4 (SD 1.8); n=26; Work and social adjustment scale 0-8 Top=High is poor outcome; Comments: Baseline values: CBT 6 (1.2), relaxation 6.1 (1.3). In paper stated that 30 in each group but known that 3 dropped out in CBT group and 4 in relaxation group. Unclear if any imputation performed by study authors so n adjusted to those attending follow up to prevent artificial reduction in SE.

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 3, Reason: 1 found CBT ineffective, 1 too ill to attend and 1 improved; Group 2 Number missing: 4, Reason: 1 too ill to attend, 1 no reason and 2 found exercises too tiring - Actual outcome for adults; severity mixed or unclear: Full or part time employment at 5 years; Group 1: 14/25, Group 2: 11/28; Comments: Hours worked per week (employed participants only): CBT 35.57 (8.11), relaxation 24 (4.97) Risk of bias: All domain – Very high, Selection – High, Blinding – High, Incomplete outcome data – Low, Outcome reporting – Low, Measurement – Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: There were some differences for use of antidepressants (CBT 13% and relaxation 27%), attribution of symptoms to physical illness (CBT 57%, relaxation 73%), age (CBT 31, relaxation 38) and illness duration (CBT 3.4 vs relaxation 4.6 years). All would favour CBT; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 2, Reason: unclear	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study	Dybwad 2007[244]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in Norway; Setting: Sunnaas Rehabilitation Hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis was made according to the CDC criteria by a medical doctor especially experienced with the condition
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Persons diagnosed with 'CFS/ME' according to the CDC criteria by a medical doctor especially experienced with the condition; minimum condition duration of two years; n=4 scored above the level set for clinical anxiety for HADS questionnaire while n=5 scored above the level set for clinical depression
Exclusion criteria	Use of anti-depressive drugs and other conditions that could give fatigue
Recruitment/selection of patients	Participants were recruited through advertisements in two of the largest newspapers in Norway.
Age, gender and ethnicity	Age - Mean (SD): 44.3 (12.8). Gender (M:F): 5/26. Ethnicity: not specified
Further population details	-

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Extra comments	59% of participants had acute illness debut vs 35% who had a gradual onset; 2% were working, 65% received full disability pension (13% of intervention group vs 50% of control group), 3% received partial disability pension (65% of intervention vs 6% of control group), 50% were in rehabilitation (13% of intervention vs 38% of control group); 97% had attended university/college; years since symptom onset (SD): 8.1 (7.3). Mean age and male/female ratio reported within text (36 years, range:17-62; 5/27) differs from what is reported in demographics table; the latter has been extracted.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=15) Intervention 1: Exercise interventions. The intervention group did Qigong exercises once a week with a certified instructor during the 6 months intervention period. Participants performed Qigong exercises for two hours a week. Each session started with 30 min group session on simple principles of anatomy and physiology followed by 1 hour of Qigong. Qigong training consisted of simple exercises containing stretches, rotations and diagonal movements. The exercise was gradually progressed to more complex movements. The last 30 minutes were left to breathing exercises, relaxation and meditation as well as non-structured conversation between the participants. Duration 6 months. Concurrent medication/care: not specified; Both groups were encouraged not to start with any new treatments in the intervention period. Indirectness: No indirectness Further details: 1. type of intervention: delivered by certified instructor (not reported whether the instructor was experienced/specialised in ME/CFS) (n=16) Intervention 2: no treatment. The control group did not do any Qigong training. Duration 6 months. Concurrent medication/care: not specified; Both groups were encouraged not to start with any new treatments in the intervention period. Indirectness: No indirectness Further details: 1. type of intervention: not applicable
Funding	Academic or government funding (EXTRA funds from the Norwegian Foundation for Health and Rehabilitation and NAFKAM.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: QIGONG versus CONTROL Protocol outcome 1: Quality of life at longest follow up available	

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- Actual outcome for adults; severity mixed or unclear: SF36- mental health at 6 months post intervention; Group 1: mean 7.2 (SD 17); n=14, Group 2: mean -5 (SD 18); n=14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: SF36- Vitality at 6 months post intervention; Group 1: mean 4.7 (SD 17); n=14, Group 2: mean 6.6 (SD 17); n=14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: SF36- Bodily pain at 6 months post intervention; Group 1: mean 13.3 (SD 25); n=14, Group 2: mean 0.4 (SD 18); n=14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: SF36-general health at 6 months post intervention; Group 1: mean -2.5 (SD 21); n=14, Group 2: mean 4.5 (SD 14); n=14; SF-36: general health 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

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- Actual outcome for adults; severity mixed or unclear: SF36-social functioning at 6 months post intervention; Group 1: mean 5 (SD 33); n=14, Group 2: mean 5.5 (SD 25); n=14; SF-36: social functioning 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: SF36-role emotional at 6 months post intervention; Group 1: mean 11.1 (SD 47); n=14, Group 2: mean -4.2 (SD 58); n=14; SF-36: role emotional 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: SF36-role physical at 6 months post intervention; Group 1: mean 3.3 (SD 30); n=15, Group 2: mean 1.6 (SD 21); n=16; SF36: role physical 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group. Baseline age, gender, illness duration similar. ; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: SF36-physical functioning at 6 months post intervention; Group 1: mean 1.3 (SD 16); n=14, Group 2: mean 4.7 (SD 13); n=14
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

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Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue severity scale at 6 months post intervention; MD; -0.5 (95%CI -0.9 to 0.02) (p-value : 0.04) 9-63 Top=High is poor outcome, Comments: MD/effect size adjusted for baseline value. Change scores: Group 1: mean -0.44 (SD 0.6); n=14; Group 2: mean 0.0 (SD 0.6); n=14.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline age, gender, illness duration similar. Baseline scores for outcome are not reported separately for the intervention and control group but result reported is adjusted for baseline values. ; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

Protocol outcome 3: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: VO2max (ml/kg/min)- as an indicator of work capacity at 6 months post intervention; MD; 3.8 (95%CI 0.9 to 6.6) (p-value: 0.01) ml/kg/min Top=High is good outcome, Comments: Adjusted for baseline value; baseline value, mean (SD) - reported for study population as a whole - 21 (7); change scores Group 1: mean 2.9 ml/kg/min (SD 6.2); n=14, Group 2: mean -1.3 ml/kg/min (SD 5.6); n=14.Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: Max work-load (Watt): maximal resistance on bicycle ergometer the patient was able to manage at 6 months post intervention; MD; 3.6 (95%CI -12 to 19) (p-value: 0.71) Top=High is good outcome, Comments: Adjusted for baseline value; baseline value, mean (SD) - reported for study population as a whole - 117 (36); change scores Group 1: mean 10 Watt (SD 15); n=14, Group 2: mean 7.3 Watt (SD 25); n=14.;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started

- Actual outcome for adults; severity mixed or unclear: Borg scale – rating of perceived exertion at 6 months post intervention; MD -2.7 (95%CI -6.2 to 0.8); 6-20, Top=High is bad outcome; change scores Group 1: mean -2 (SD 6); n=14, Group 2: mean 0.1 (SD 2); n=14; Comments: Registered at the end of

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each stage, MD adjusted for baseline values; baseline value reported for study population as a whole - mean 18 (SD 2). Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline scores for outcome are not reported separately for the intervention and control group; Group 1 Number missing: 1, Reason: n=1 had a fractured leg; n=1 had a bad experience from the baseline testing because of aggravation of symptoms; Group 2 Number missing: 2, Reason: patient became ill early in the intervention period and withdrew before the training period started	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study (subsidiary papers)	FatiGo trial: Vos-Vromans 2016[808] (Vos-Vromans 2017[807], Vos-Vromans 2012[809])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=122)
Countries and setting	Conducted in Netherlands; Setting: Four rehabilitation centres
Line of therapy	Unclear
Duration of study	Intervention + follow up: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: consultant confirmed the inclusion and exclusion criteria and verified whether an extensive physical examination and laboratory research tests had been performed to exclude any underlying illness. An interview with a psychologist was scheduled if the HADS depression subscale score was 11 or more (to exclude a major or bipolar depressive disorder) or if the consultant suspected another psychiatric illness or motivational problem.
Stratum	adults; severity mixed or unclear: age between 18 and 60 years; meeting CDC criteria, Checklist Individual Strength fatigue subscale score of 40 or more - no further detail on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Met the US Centers for Disease Control and Prevention (CDC-94) criteria for CFS; a Checklist Individual Strength fatigue subscale score of 40 or more; willingness to participate in a treatment aimed at changing behaviour; age between 18 and 60 years and comprehension of written and verbal Dutch
Exclusion criteria	Medical condition explaining the presence of chronic fatigue; psychotic, major or bipolar depressive disorder, dementia, anorexia, bulimia nervosa or a body mass index ≥45 kg m 2; alcohol and/or drug abuse; pregnancy; already received CBT or MRT for CFS in the past; had to travel for more than 1 h to the nearest participating rehabilitation centre

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Recruitment/selection of patients	Patients referred to 4 rehabilitation centres meeting eligibility criteria during the recruitment period
Age, gender and ethnicity	Age - Mean (SD): multidisciplinary rehabilitation 40 (10.2), CBT 40.6 (12) years. Gender (M:F): 25/97. Ethnicity: country of birth The Netherlands n=110, other European country n=6, country outside Europe n=4
Further population details	-
Extra comments	In some regions in the Netherlands, the incidence of Q fever increased during the trial. As Q fever can cause similar symptoms to those of CFS, patients from high-risk regions were additionally tested for Q fever and excluded from the study in case of a positive diagnosis.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=62) Intervention 1: Psychological and behavioural interventions - pragmatic rehabilitation. Patient-centred and based on addressing modifiable components that are related with the precipitation, predisposition and perpetuation of CFS. Observational phase: thorough assessment (interview, physical examination, baseline assessment and goal setting) by an interdisciplinary team (physical therapist, occupational therapist, psychologist and social worker) over 2 weeks (total contact time 8.5 h). Followed by 2 weeks without treatment in which the therapists and the consultant in rehabilitation medicine discussed findings, defined the treatable components and proposed treatment. 10 week treatment phase: individual sessions (total contact time 33 h), weekly visits to the PT and OT and biweekly visits to the psychologist and social worker. Included CBT and, depending on the individual analysis, elements of body awareness therapy, gradual reactivation, pacing, mindfulness, gradual normalization of sleep/wake rhythm and social reintegration. PT and OT focused on the gradual reactivation of the patient by increasing activities under supervision. PT focused on body awareness therapy, aiming to establish increased awareness and consciousness of the body and its relation to psychological well-being. PT and OT taught patient to pace activities and avoid bursts of extreme activity followed by extreme fatigue. Patient coached to reintegrate into society by making a plan to return to work or school and increase social activities. Psychologist and OT addressed the gradual normalization of a patient's sleep/wake rhythm. According to CBT principles, the psychologist focused on modification of dysfunctional beliefs regarding illness symptoms, activity, self-expectations and self-esteem and the development of more effective coping strategies. Every therapist followed the principles of CBT and incorporated them with mindfulness principles. Interdisciplinary team

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	meetings scheduled to discuss progress. Follow-up phase (12weeks): patients returned for 2 days to meet with the social worker and 2 therapists of their choice. Issues of social reintegration and participation discussed and patients encouraged to continue using the principles learned. Most therapists had experience in treating patients with chronic pain and/or chronic fatigue and familiar with CBT. They received training for each discipline (3–5 day) and attended 2 team meetings and 2 supervision meetings for each discipline during the trial. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (Most therapists had experience in treating patients with chronic pain and/or chronic fatigue; MRT tailored to CFS). (n=60) Intervention 2: Psychological and behavioural interventions - CBT. Through dialogue with the psychologist or behavioural therapist and implementation during home exercises, patients taught to change negative beliefs regarding symptoms of fatigue, self-expectation and self-esteem. Patients also encouraged to adopt a regular sleep/wake rhythm. Time-contingent schedules made to gradually increase physical activity at home. 16 x 45-60 min sessions, over 6 months. Weekly contact with the psychologist or behavioural therapist for 6 weeks, followed by biweekly contact for next 20 weeks. Protocol specifically tailored for either relatively active or passive patients. Relatively active patients started by practicing at an activity level in which an increase of symptoms is avoided. For passive patients, physical activities were gradually increased from the beginning of therapy. Therapists were experienced in treating patients with complaints of chronic pain and/or chronic fatigue, familiar with CBT and attended a 3-day course to familiarize themselves with the CBT protocol for CFS. Five supervision meetings were held and therapists were able to contact the supervisor as needed. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (Therapists were experienced in treating patients with complaints of chronic pain and/or chronic fatigue, CBT tailored to CFS).
Funding	Other (Netherlands Organisation for Health Research and Development, Rehabilitation Fund, Foundation Nutsohra and ME/CVS Stichting Nederland)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIDISCIPLINARY REHABILITATION versus CBT

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical component summary at 52 weeks; MD; 2.67 (95%CI -1.45 to 6.79) (p value : 0.2)
SF36 physical component summary 0-100 Top=High is good outcome, Comments: Baseline values: MRT 30.59 (7.93), CBT 32.6 (7.78)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance)
n=112 (55 CBT, 57 MRT)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

- Actual outcome for adults; severity mixed or unclear: SF36 mental component summary at 52 weeks; MD; 1.59 (95%CI -1.96 to 5.13) (p value : 0.38)
SF36 mental component summary 0-100 Top=High is good outcome, Comments: Baseline values: MRT 46.57 (9.23), CBT 44.38 (9.02)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance)
n=112 (55 CBT, 57 MRT)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile 8 at 52 weeks; MD; 50.78 (95%CI -186.68 to 288.24) (p value : 0.67)
Sickness Impact Profile 8 0-6160 Top=High is poor outcome, Comments: Baseline values: MRT (1418.27 (614.24), CBT 1222.17 (633.53)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance)
n=112 (55 CBT, 57 MRT)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment; Group 2 Number missing: 5, Reason: 2

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lost to follow up, 3 withdrew from assessment

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual Strength - fatigue severity at 52 weeks; MD; -5.69 (95%CI -10.62 to -0.76) (p value : 0.02) Checklist Individual Strength 8-56 Top=High is poor outcome, Comments: Baseline values: MRT 51.47 (5.08), CBT 51.05 (5.09)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance)
n=112 (55 CBT, 57 MRT)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Symptom Checklist 90 at 52 weeks; MD; -7.83 (95%CI -19.84 to 4.19) (p value : 0.2) Symptom Checklist 90 90-450 Top=High is poor outcome, Comments: Baseline values: MRT 158.73 (39.86), CBT 163.87 (34.4)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance)
n=112 (55 CBT, 57 MRT)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing: 5, Reason: 1 lost to follow up, 4 withdrew from assessment; Group 2 Number missing: 5, Reason: 2 lost to follow up, 3 withdrew from assessment

Protocol outcome 5: Activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Accelerometer at 52 weeks; MD; 2009.58 (p value : 0.85), Comments: Reported CIs: -19140.04 - 23159.19
Baseline values: MRT 206233.65 (40264.16), CBT 202033.66 (43379.41)
Estimated differences between groups calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance)
accelerometer registers the peak acceleration (in counts) every minute in two directions (longitudinal and transverse axis). A count is a measure of frequency and intensity of acceleration and deceleration (with higher counts indicating a higher degree of physical activity).

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n=80. Skin rash and unwillingness to either wear the monitor or travel to the rehabilitation centre to collect the monitor were the main reasons for not providing activity monitor data Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographic and clinical characteristics at referral; Group 1 Number missing:; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	FINE trial: Wearden 2010[834] (Wearden 2013[835], Wearden 2006[837])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=296)
Countries and setting	Conducted in United Kingdom; Setting: 186 GP practices across north west England
Line of therapy	Unclear
Duration of study	Intervention + follow up: 70 weeks (18 weeks treatment)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Meeting Oxford diagnostic criteria. GP referred in accordance with a brief diagnostic protocol and checklist which included a list of exclusionary tests.
Stratum	adults; severity mixed or unclear: Age ≥ 18 years; scored ≤ 70% on SF-36 physical functional scale and ≥ 4 on Chalder fatigue scale at baseline; 11% of participants said to be non-ambulatory at baseline (used mobility aid on most days)
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Age ≥ 18 years; fulfilled Oxford criteria for ME/CFS; scored ≤ 70% of SF-36 physical functional scale; scored ≥ 4 on Chalder fatigue scale
Exclusion criteria	Fatigue explained by any active medical condition; fulfilled diagnostic criteria for antisocial, borderline, or paranoid personality disorder; active suicidal ideation; unable to read or write English; currently undertaking systematic psychological therapies for 'CFS/ME', or had received pragmatic rehab in the past year.
Recruitment/selection of patients	Patients from participating GP practices referred by their GP
Age, gender and ethnicity	Age - Mean (range): pragmatic rehab 44.74 (18-68); supportive listening 45.13 (21-68); usual care 44.92 (18-71). Gender (M:F): 66/230. Ethnicity: Not reported

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Further population details	-
Extra comments	Illness duration median 7 years (range 0.5-51); pragmatic rehab/supportive listening/usual care: Townsend deprivation score (median (range)) 1.5 (-6-13)/0 (-7-13)/0.5 (-7-13); self-reported medical comorbidities (%) 0 - 44.2/38.6/33, 1 - 22.1/28.7/24.0, ≥2 33.7/32.7/43.0; met London ME criteria (%) 29.5/30.7/33; any anxiety diagnosis (%) 26.66/20/25.6; any depression diagnosis (%) 18.9/14.9/20; ambulatory (%) 89.5/57.1/88.
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=95) Intervention 1: Psychological and behavioural interventions - pragmatic rehabilitation. 10 pragmatic rehabilitation sessions over an 18 week period. A programme of graded return to activity is designed collaboratively by the patient and the therapist on the basis of a physiological dysregulation model of ME/CFS. The programme encourages patients to regularise sleep patterns and includes relaxation exercises to address the somatic symptoms of anxiety. A further component addresses concentration and memory problems. Session 1- patients given detailed explanation of symptoms, supported by a referenced manual with diary pages. Session 2 - manual reviewed and patient priorities determined and goals set at an easily manageable level. Session 3-10 - progress reviewed and programme adjusted if needed. Session 5-10 - relapse prevention discussion, model of 'CFS/ME' contained in manual reinforced. 90 minute home visit in week 1; one hour home visits on weeks 2, 4, 10, 19; and 30 minute phone calls weeks 3, 6, 8, 12, 15. Treatment delivered in patients' homes by registered, adult specialty, general nurses who had worked in primary care but had no previous experience with ME/CFS. All sessions were taped. Duration 18 weeks. Concurrent medication/care: Patients were free to consult their GP during the course of treatment. Median (range) consultations with GP during treatment period: 2 (0-14). At baseline: n=51 prescribed antidepressant; n=30 prescribed analgesic. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: other interventions (Treatment delivered by registered, adult specialty, general nurses who had worked in primary care but had no previous experience with ME/CFS. Training was provided by members of the trial team over 4 months (16 half days). Fortnightly supervision of therapists was provided). (n=101) Intervention 2: Psychological and behavioural interventions - counselling. 10 supportive listening sessions over an 18 week period. Therapy based on non-directive counselling in which the therapist aims to

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	provide an empathic and validating environment in which the patient can discuss his or her concerns and work towards resolution of whichever problems the patient wishes to prioritise. Session 1- basis of therapeutic approach explained patients received short booklet with diary pages. Issues for discussion in subsequent sessions elicited. Therapists used standard counselling techniques of active listening, reflection and summarising to ensure patients felt understood. Sessions 2-10 - previous sessions summarised by therapist and patient invited to set agenda for current session. Therapists did not provide any explanation for patient's symptoms. Content of sessions determined by patients and therapists avoided giving advice or leading patients; focus on providing an empathic validating environment in which patients could discuss their concerns. 90 minute home visit in week 1; one hour home visits on weeks 2, 4, 10, 19; and 30 minute phone calls weeks 3, 6, 8, 12, 15. Treatment delivered in patients' homes by registered, adult specialty, general nurses who had worked in primary care but had no previous experience with ME/CFS. All sessions were taped. Duration 18 weeks. Concurrent medication/care: Patients were free to consult their GP during the course of treatment. Median (range) consultations with GP during treatment period: 3 (0-23). At baseline: n=60 prescribed antidepressant; n=22 prescribed analgesic. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: other interventions (Treatment delivered by registered, adult specialty, general nurses who had worked in primary care but had no previous experience with ME/CFS. Training was provided by experienced counsellor over 4 months (16 half days. Fortnightly supervision of therapists was provided.). (n=100) Intervention 3: usual care - standard medical care. GPs were asked to manage their cases as they saw fit, but not to refer for systematic psychological therapies for 'CFS/ME' during the 18 week treatment period. Duration 18 weeks. Concurrent medication/care: Median (range) consultations with GP during treatment period: 3 (0-16). At baseline: n=49 prescribed antidepressant; n=27 prescribed analgesic. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (UK medical research council; UK department of health; University of Manchester)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAGMATIC REHABILITATION versus SUPPORTIVE LISTENING

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder's fatigue scale at 70 weeks; Group 1: mean 8.72 (SD 3.65); n=81, Group 2: mean 9.39 (SD 3.21); n=90; Chalder's fatigue scale (11-item, bimodal scoring) 0-11 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 10.49 (1.12); supportive listening 10.52 (1.03)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern)

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 - physical functioning subscale at 70 weeks; Group 1: mean 43.27 (SD 27.38); n=81, Group 2: mean 35.72 (SD 25.94); n=90; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 29.84 (17.86); supportive listening 30.64 (19.04)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern)

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety subscale at 70 weeks; Group 1: mean 9.54 (SD 4.7); n=81, Group 2: mean 9.62 (SD 4.87); n=90; Hospital anxiety and depressions scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 11.02 (4.77); supportive listening 10.80 (5.12)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number

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missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern)

- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression subscale at 70 weeks; Group 1: mean 7.88 (SD 4.45); n=81, Group 2: mean 8.67 (SD 4.51); n=90; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 9.97 (4.08); supportive listening 9.73 (4.07)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern)

Protocol outcome 4: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 70 weeks; Group 1: mean 12.32 (SD 5.61); n=81, Group 2: mean 13.18 (SD 5.71); n=90; Jenkins sleep scale 0-20 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 14.11 (4.88); supportive listening 14.30 (4.75)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAGMATIC REHABILITATION versus GP TREATMENT AS USUAL

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder's fatigue scale at 70 weeks; Group 1: mean 8.72 (SD 3.65); n=81, Group 2: mean 9.48 (SD 2.71); n=86; Chalder's fatigue scale (11-item, bimodal scoring) 0-11 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 10.49 (1.12); usual care 10.34 (1.17)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 - physical functioning subscale at 70 weeks; Group 1: mean 43.27 (SD 27.38); n=81, Group 2: mean 39.83 (SD 27.77); n=86; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 29.84 (17.86); usual care 29.80 (19.63)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety subscale at 70 weeks; Group 1: mean 9.54 (SD 4.7); n=81, Group 2: mean 8.89 (SD 5.4); n=85; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 11.02 (4.77); usual care 9.65 (5.06)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression subscale at 70 weeks; Group 1: mean 7.88 (SD 4.45); n=81, Group 2: mean 8.06 (SD 4.75); n=85; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 9.67 (4.08); usual care 9.26 (4.25)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

Protocol outcome 4: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 70 weeks; Group 1: mean 12.32 (SD 5.61); n=81, Group 2: mean 12.63 (SD 5.34); n=86; Jenkins sleep scale 0-20 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: pragmatic rehab 14.11 (4.88); usual care 12.85 (4.96)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 14, Reason: lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

Protocol outcome 5: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Step-test - number of steps completed at 70 weeks; Group 1: mean 19.1 (SD 3.59); n=42, Group 2: mean 19.31 (SD 2.21); n=29; Top=High is good outcome; Comments: Baseline scores, mean (SD): pragmatic rehab n=77, 18.49 (3.81); usual care n=77, 18.31 (4.1); Step-test: Patients asked to step on and off a 20cm step "at a normal pace". In the event the patient reached subjective exhaustion before completing 20 steps, the time taken, and number of steps completed was recorded.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar. ; Blinding details: Objective outcome, however result may be affected by knowledge of intervention due to effort required; Group 1 Number missing: 53, Reason: n=14 lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); n=32 unwilling to attempt step-test; n=7 unclear; Group 2 Number missing: 71, Reason: n=14 lost to follow-up (n=8 declined, n=6 no response); n=45 unwilling to attempt step-test; n=12 unclear

- Actual outcome for adults; severity mixed or unclear: Step-test - time taken to complete steps at 70 weeks; Group 1: mean 49.9 seconds (SD 11.81); n=41, Group 2: mean 54.67 (SD 14.15); n=30; Top=High is poor outcome; Comments: Baseline scores, mean (SD): pragmatic rehab n=77, 63.91 (19.47);

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usual care n=77, 61.58 (16.44); Step-test: Patients asked to step on and off a 20cm step "at a normal pace". In the event the patient reached subjective exhaustion before completing 20 steps, the time taken, and number of steps completed was recorded.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar. ; Blinding details: Objective outcome, however result may be affected by knowledge of intervention due to effort required; Group 1 Number missing: 52, Reason: n=14 lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); n=32 unwilling to attempt step-test; n=8 unclear; Group 2 Number missing: 70, Reason: n=14 lost to follow-up (n=8 declined, n=6 no response); n=45 unwilling to attempt step-test; n=11 unclear

- Actual outcome for adults; severity mixed or unclear: Borg rating of perceived exertion (VAS) at 70 weeks; Group 1: mean 11.73 (SD 1.91); n=41, Group 2: mean 11.87 (SD 2.21); n=30; Borg rating of perceived exertion (VAS) 6-20 Top=High is poor outcome; Comments: Baseline scores, mean (SD): pragmatic rehab n=76, 12.75 (2.72) ; usual care n=77, 12.65 (2.58);
Visual analogue scale with 7 points labeled: 7=very, very light; 19=very, very hard.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar. ; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 52, Reason: n=14 lost to follow-up (n=10 declined, n=3 no response, n=1 researcher safety concern); n=32 unwilling to attempt step-test; n=8 unclear; Group 2 Number missing: 70, Reason: n=14 lost to follow-up (n=8 declined, n=6 no response); n=45 unwilling to attempt step-test; n=11 unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SUPPORTIVE LISTENING versus GP TREATMENT AS USUAL

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder's fatigue scale at 70 weeks; Group 1: mean 9.39 (SD 3.21); n=90, Group 2: mean 9.48 (SD 2.71); n=86; Chalder's fatigue scale (11-item, bimodal scoring) 0-11 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: supportive listening 10.52 (1.03); usual care 10.34 (1.17)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory

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status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 - physical functioning subscale at 70 weeks; Group 1: mean 35.72 (SD 25.94); n=90, Group 2: mean 39.83 (SD 27.77); n=86; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD), all randomised: supportive listening 30.64 (19.04); usual care 29.80 (19.63)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety subscale at 70 weeks; Group 1: mean 9.62 (SD 4.87); n=90, Group 2: mean 9.65 (SD 5.06); n=85; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: supportive listening 10.80 (5.12); usual care 9.65 (5.06)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern); Group 2 Number missing: 15, Reason: lost to follow-up (n=8 declined, n=6 no response); n=1 not reported

- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression subscale at 70 weeks; Group 1: mean 8.67 (SD 4.51); n=90, Group 2: mean 8.06 (SD 4.75); n=85; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: supportive listening 9.73 (4.07); usual care 9.26 (4.25)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory

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status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern); Group 2 Number missing: 15, Reason: lost to follow-up (n=8 declined, n=6 no response); n=1 not reported Protocol outcome 4: Sleep quality at longest follow up available - Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 70 weeks; Group 1: mean 13.18 (SD 5.71); n=90, Group 2: mean 12.63 (SD 5.34); n=86; Jenkins sleep scale 0-20 Top=High is poor outcome; Comments: Baseline scores (SD), all randomised: supportive listening 14.30 (4.75); usual care 12.85 (4.96) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation stratified based on patient ambulatory status (using mobility aid most days) and whether or not patients fulfilled London ME criteria; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Gender, age, ambulatory status, and a number of other factors comparable. Baseline scores similar; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 11, Reason: lost to follow-up (n=6 declined, n=4 no response, n=1 researcher safety concern); Group 2 Number missing: 14, Reason: lost to follow-up (n=8 declined, n=6 no response)	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study	Friedberg 2016[269]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=137)
Countries and setting	Conducted in USA; Setting: Home
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients primarily obtained from CFS-specialised physicians with large tertiary care practices in the USA, however study was also advertised in patient newsletters and websites. Meeting Fukuda 1994 symptom/impairment criteria for CFS. Patients were screened by a nurse over the phone for exclusionary medical conditions, so did not have a physical examination. They were asked to provide a note from their physicians confirming a diagnosis of CFS but only 47% of participants did this.
Stratum	adults - severe: Age 18-65; study author reported participants were severely affected.
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Aged 18-65 years; not pregnant; physically capable of doing self-management program; at least 6 months of persistent, unremitting fatigue; meeting Fukuda 1994 symptom and impairment criteria for CFS, including at least 6 months of persistent fatigue and 4/8 secondary symptoms.
Exclusion criteria	Medical exclusions consisted of cases of fatigue clearly attributable to self-report medical conditions (such as untreated hypothyroidism, unstable diabetes, chronic infections, or AIDS). Exclusionary psychiatric conditions included self-reported psychosis, substance or alcohol abuse in 2 years prior to illness onset or any time after, current or past depression with melancholic or psychotic features within 5 years prior to illness onset or any time after.

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Recruitment/selection of patients	Patients primarily recruited from 5 CFS-specialised physicians with large tertiary care practices in the USA, however study was also advertised in patient newsletters and websites.
Age, gender and ethnicity	Age - Mean (SD): FSM:ACT 48.01 (12.43); FSM:CTR 46.99 (10.79); usual care 50.03 (11.28) years. Gender (M:F): 16/121. Ethnicity: 92% white
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=89) Intervention 1: self-management - self-management programmes. 2 fatigue self-management programmes with slight differences (as below). They involved no face-to-face visits or clinical contacts with an interventionist. The program (delivered by booklet and audio CDs) educated the participant about diagnosis, possible causal factors in CFS; stress factors and behaviours that play a role in disturbed sleep patterns, post-exertional symptoms, and push-crash activity cycles. Persistent fatigue was explained as a symptom associated with doing too much or too little. Optimal self-management intended to provide healthy balance between mental and physical exertion and rest. Daily diary used to identify baseline activities, symptoms, stress levels. Self-management text showed participants how to identify unhelpful behaviours and beliefs about illness followed by the development of more useful cognitive and behavioural coping strategies. Program encouraged individualised self-scheduling of home-based assignments, sleep-rest assignments and coping skills. The final topic was post-intervention planning for maintenance of new skills. Duration: 3months 1. Fatigue self-management with actigraphs and web diaries (FSM:ACT). Participants received a 56 page self-management booklet and 2 audio CDs that duplicated the booklet. A relaxation audio CD was also included. Daily online web diaries were assigned to monitor fatigue and track compliance with the program. Actigraphs were worn 24/7 for 1 week at baseline, and at 3 month and 12 month follow-ups. Actigraphs were used for research purposes, and not to assist the intervention. Duration: 3 months 2. Fatigue self-management with step counters and paper diaries (FSM:CTR). Participants received the same self-management program as the FSM:ACT group but with the following differences. Daily paper diaries (converted to paper from web diary forms used in FSM:ACT) were assigned to monitor fatigue. Pedometers were worn 24/7 except when sleeping or bathing at the 1 week assessment periods (baseline, 3 month and 12 month follow-ups).Subjects recorded number of steps indicated on the step counter at the end of each

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	assessment day. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Other intervention: content specific to ME/CFS but self-delivered Comments: 2 types of self-management programme combined (n=48) Intervention 2: usual care - standard medical care. Consisted of patient's usual care (not further specified). Participants filled out daily online web diary and wore actigraphs during 1 week assessment periods only (baseline, and 3 month and 12 month follow-ups). Actigraphs were used for research purposes, and not to assist the intervention. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not Applicable
Funding	Academic or government funding (National Institute of Nursing Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-MANAGEMENT PROGRAMMES versus USUAL CARE/NO TREATMENT CONTROL

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults - severe: Fatigue severity scale at 12 months ; Group 1: mean 6.05 (SD 0.8); n=78, Group 2: mean 6.42 (SD 0.8); n=46; fatigue severity scale Top=High is poor outcome; Comments: Baseline values: self-management 6.49 (0.5), usual care 6.62 (0.48)
SDs calculated from SEs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 11, Reason: unclear ; Group 2 Number missing: 2, Reason: unclear

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults - severe: SF36 physical function at 12 months ; Group 1: mean 46.13 (SD 23.3); n=80, Group 2: mean 44.07 (SD 23.3); n=45; SF36 physical function 0-100 Top=High is good outcome; Comments: Baseline values: self-management 37.75 (20.2), usual care 45.77 (20.3)
SDs calculated from SEs
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: unclear ; Group 2 Number missing: 3, Reason: unclear

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Protocol outcome 3: Psychological status at longest follow up available - Actual outcome for adults - severe: Beck depression inventory at 12 months ; Group 1: mean 13.75 (SD 9.42); n=80, Group 2: mean 18.64 (SD 9.3); n=45; Beck depression inventory 0-63 Top=High is poor outcome; Comments: Baseline values: self-management 18.53 (10.79), usual care 20.38 (10.6) SDs calculated from SEs Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: unclear ; Group 2 Number missing: 3, Reason: unclear - Actual outcome for adults - severe: Beck anxiety inventory at 12 months ; Group 1: mean 15.8 (SD 10.36); n=78, Group 2: mean 18.3 (SD 10.3); n=43; Beck anxiety inventory 0-63 Top=High is poor outcome; Comments: Baseline values: self-management 17.59 (10.36), usual care 18.84 (10.3) SDs calculated from SEs Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 11, Reason: unclear ; Group 2 Number missing: 5, Reason: unclear	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Fukuda 2016[274]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=43)
Countries and setting	Conducted in Japan; Setting: Single centre, outpatient
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients who were diagnosed with CFS according to 1994 CDC criteria
Stratum	adults; severity mixed or unclear: Age >20 years; no info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients diagnosed with CFS according to 1994 CDC criteria; age >20. Patients who had been on ubiquinol before recruitment were included after a washout period of at least 4 weeks.
Exclusion criteria	Diseases that induce fatigue; pregnancy or lactation; allergies to certain materials (e.g. soft capsules); physician determined ineligibility for various reasons
Recruitment/selection of patients	Patients who had visited a single university hospital outpatient clinic and were diagnosed with CFS
Age, gender and ethnicity	Age - Mean (SD): ubiquinol 34.8 (9.36) years; placebo 39.5 (8.5) years. Gender (M:F): 7/25. Ethnicity: Not reported
Further population details	-

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Extra comments	Population details reported are in analysed population (patients randomised who completed treatment, ubiquinol n=17 and placebo n=14) M/F ratio in placebo group reported as 3/12 (inconsistent with no. in analysed group), hence inconsistency in extracted M/F ratio for study.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=21) Intervention 1: dietary supplementation - co-enzyme Q10. Capsules containing ubiquinol-10, provided by Kaneka, 50mg in each capsule. 3 capsules (150mg) taken daily after a meal. Supplementation time and methods were left to patient's discretion. Duration 12 weeks. Concurrent medication/care: n=5 took vitamin C supplements; n=3 on psychoactive medications. All patients instructed not to take CoQ10 supplements 4 weeks before pre-intervention test. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=22) Intervention 2: placebo or sham - placebo/sham. Capsules containing placebo, provided by Kaneka (not further described). 3 capsules daily after a meal. The supplementation time and methods were left to the patient's discretion. Duration 12 weeks. Concurrent medication/care: n=9 took vitamin C supplements; n=1 on psychoactive medications. All patients instructed not to take CoQ10 supplements 4 weeks before pre-intervention test. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Other (Kaneka Inc (industry) provided study grants to main authors, partly funded study, and provided study drugs; Ministry of Health, Labour and Welfare (government) partly funded study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: UBIQUINOL-10 (CO-ENZYME Q10) versus PLACEBO

Protocol outcome 1: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Uchida-Kraepelin psychodiagnostic test - number of responses at 12 weeks; Group 1: mean 222.9 (SD 74.63); n=17, Group 2: mean 217.2 (SD 65.48); n=14. Comments: Baseline scores, mean (SD): ubiquinol 202.2 (76.28); placebo 216.9 (66.98); standard deviations calculated from standard error. 5 minute arithmetic task; consisted of a series of addition questions with single digit figures that were displayed on a computer screen. Subjects selected a number on a computer keypad that corresponded to their answer.

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Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation - block randomisation stratified by age, sex, psychiatric comorbidity - no further details. Outcome reporting - correct rate and response time per question results for Uchida-Kraepelin test reported only as not statistically significant; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline age, sex, CES-D score, Chalder fatigue score, CoQ10 levels similar. Baseline scores similar.; Group 1 Number missing: 4, Reason: n=1 discontinued intervention due to deconditioning (not further explained); n=3 did not receive intervention (n=2 withdrew consent, n=1 deconditioning); Group 2 Number missing: 8, Reason: n=2 discontinued intervention due to breaking rules or not participating in test; n=6 did not receive intervention (n=3 withdrew consent, n=2 deconditioning, n=1 diarrhoea prior to receiving treatment)

- Actual outcome for adults; severity mixed or unclear: Uchida-Kraepelin psychodiagnostic test - number of correct responses at 12 weeks; Group 1: mean 216 (SD 76.28); n=17, Group 2: mean 211.9 (SD 66.98); n=14. Comments: Baseline scores, mean (SD): ubiquinol 197.4 (77.51); placebo 212.4 (68.10); standard deviations calculated from standard error. 5 minute arithmetic task; consisted of a series of addition questions with single digit figures that were displayed on a computer screen. Subjects selected a number on a computer keypad that corresponded
to their answer.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation - block randomisation stratified by age, sex, psychiatric comorbidity - no further details. Outcome reporting - correct rate and response time per question results for Uchida-Kraepelin test reported only as not statistically significant. ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline age, sex, CES-D score, Chalder fatigue score, CoQ10 levels similar. Baseline scores similar.; Group 1 Number missing: 4, Reason: n=1 discontinued intervention due to deconditioning (not further explained); n=3 did not receive intervention (n=2 withdrew consent, n=1 deconditioning); Group 2 Number missing: 8, Reason: n=2 discontinued intervention due to breaking rules or not participating in test; n=6 did not receive intervention (n=3 withdrew consent, n=2 deconditioning, n=1 diarrhoea prior to receiving treatment)

Protocol outcome 2: adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Serious adverse events at 12 weeks; Group 1: 0/18, Group 2: 0/16; Comments: Serious adverse events including hospitalisations related to study intervention
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation - block randomisation stratified by age, sex, psychiatric comorbidity - no further details. Incomplete outcome - number analysed in safety analysis not clearly reported, but likely all participants who received treatment.
; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline age, sex, CES-D score, Chalder fatigue score, CoQ10 levels similar. Medical comorbidities not reported; Blinding details: Unclear who outcome assessor is, so unclear if blinded. Medical staff and patients reported to be blinded. Placebo not described in detail - unclear if identical to active treatment. ; Group 1 Number missing: , Reason: n=1 discontinued intervention due

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to deconditioning (not further explained); n=3 did not receive intervention (n=2 withdrew consent, n=1 deconditioning); Group 2 Number missing: , Reason: n=2 discontinued intervention due to breaking rules or not participating in test; n=6 did not receive intervention (n=3 withdrew consent, n=2 deconditioning, n=1 diarrhoea prior to receiving treatment)	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Fulcher 1997[275]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in United Kingdom; Setting: secondary care (outpatients referred to chronic fatigue clinic at general hospital department of psychiatry)
Line of therapy	Unclear
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Oxford criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients referred to chronic fatigue clinic in general hospital of psychiatry, meeting Oxford criteria for chronic fatigue syndrome, for which other disorders had been excluded. Patients with ME/CFS who also had a psychiatric disorder or insomnia were offered treatment for their comorbid disorder and if this was successful but still met criteria for ME/CFS, they were recruited into the trial.
Exclusion criteria	Patients with current psychiatric disorder or symptomatic insomnia (assessed using structured clinical interview for the DSM-III-R)
Recruitment/selection of patients	Not specified; number of patients specified by power calculation to allow 10% drop-out.
Age, gender and ethnicity	Age - Mean (SD): 37.2 (10.7). Gender (M:F): 17/49. Ethnicity: Not specified

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Further population details	
Extra comments	Mean illness duration (range): 2.7 (0.6-19) years; n=20 were taking full dose antidepressants; n=10 were taking low dose tricyclic anti-depressants as hypnotics; 27 (41%) had successfully been treated for a comorbid disorder beforehand but still met criteria for 'chronic fatigue syndrome'
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=33) Intervention 1: Exercise interventions - GET. Patients attended weekly for 12 weeks of supervised treatment and the next week's exercise prescription. All laboratory sessions were supervised by an exercise physiologist using basic principles of exercise prescription, adapted for the patients' current's capacity. Home exercise was prescribed on at least five days a week, with initial sessions lasting between five and 15 minutes at an intensity of 40% of peak oxygen consumption (roughly 50% of the maximum recorded heart rate). The daily exercise prescription was increased by one or two minutes (negotiated with the patient each week) up to a minimum of 30 minutes. The intensity of the exercise was then increased to a maximum of 60% of peak oxygen consumption. Patients were given ambulatory heart rate monitors to ensure that they reached but did not exceed target heart rates. The main exercise was walking but patients were encouraged to take other modes of exercise such as cycling and swimming. Patients were advised not to exceed prescribed exercise during a good phase. If patients complained of increased fatigue they were advised to continue at the same level of exercise for an extra week and increase when fatigue had lessened. Duration 12 weeks. Concurrent medication/care: Of all patients included in the study, n=20 were taking full dose anti-depressants; n=10 were taking low dose tricyclic anti-depressants as hypnotics. All were told to continue their medication unchanged. Indirectness: No indirectness Further details: 1. type of intervention: supervised by an exercise physiologist, unclear whether they were experienced/specialised in ME/CFS (n=33) Intervention 2: Exercise interventions - physical rehabilitation. Flexibility and relaxation sessions were provided by the same exercise physiologist. Each patient was taught a stretching routine and relaxation techniques. Patients were encouraged to start with sessions of 10 minutes increasing to 30 minutes a day every five days a week as more stretching exercises were added. They were specifically told to avoid doing any extra physical activities. Patients kept a weekly activity diary, recording the type, duration and response to exercise or stretching, which determined the next week's prescription. Duration 12 weeks. Concurrent

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	medication/care: Of all patients included in the study, n=20 were taking full dose anti-depressants; n=10 were taking low dose tricyclic anti-depressants as hypnotics. All were told to continue their medication unchanged. Indirectness: No indirectness; Indirectness comment: none Further details: 1. type of intervention: supervised by an exercise physiologist, unclear whether they were experienced/specialised in ME/CFS
Funding	Other (Lindbury Trust, a Sainsbury charitable trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus FLEXIBILITY TREATMENT

Protocol outcome 1: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical global impression change score (overall change score compared with study onset, score between 1 and 7, where 1='very much better', 7='very much worse', 4='no change') at after treatment completion (12 weeks); Group 1: 16/29, Group 2: 8/30; Comments: The outcome was analysed categorically, a score of 1 or 2 ('very much better' or 'much better' being considered clinically important versus scores of 3 to 7 ('a little bit better' to 'very much worse'. Hence participants with a score 1 or 2 are considered clinically improved and extracted as the number of events for the purpose of this analysis.
n=7 participants (four in the exercise group and three in the flexibility group) did not attend the psychiatrist (outcome assessor) at the correct time despite completing treatment; these patients assessed their clinical global impression score retrospectively and returned it by post.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: Participants and caregivers were not blind due the different nature of the interventions; the outcome was subjective but the outcome assessors were blind to the intervention, however clinicians judgements are likely based on participant responses therefore high risk of bias; Group 1 Number missing: 4, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated; Group 2 Number missing: 3, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue score (normal/usual score: 14) at after treatment completion (12 weeks); Group 1: mean 20.5 (SD 8.9); n=29, Group 2: mean 27.4 (SD 7.4); n=30; Chalder fatigue score (14 items) 0-42 Top=High is poor outcome; Comments: Normal or usual score is 14
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness; Blinding details: It was not possible to blind participants and caregivers to treatment allocation due the different nature of the interventions. Considering this was a subjective, self-rated outcome, knowledge of

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the intervention may have led to bias in self-rated scores. ; Group 1 Number missing: 4, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated; Group 2 Number missing: 3, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated Protocol outcome 3: Physical functioning at longest follow up available - Actual outcome for adults; severity mixed or unclear: SF-36 physical function score at after treatment completion (12 weeks); Group 1: mean 69 (SD 18.5); n=29, Group 2: mean 55 (SD 21.8); n=30; SF-36 physical function 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: It was not possible to blind participants and caregivers to treatment allocation due the different nature of the interventions. Considering this was a subjective, self-rated outcome, knowledge of the intervention may have led to bias in self-rated scores; Group 1 Number missing: 4, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated; Group 2 Number missing: 3, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated Protocol outcome 4: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Treadmill walking test duration (min) at after treatment completion (12 weeks); Group 1: mean 12.4 minute (SD 3.5); n=29, Group 2: mean 11 minute (SD 3.3); n=30; Comments: A treadmill walking test was carried out at a constant 5km/h, the slope being increased every two minutes; all patients were encouraged to continue the test to their maximum. Both available case and intention to treat analysis results are reported in the paper. Available case analysis results are extracted. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: Participants and caregivers were not blind due the different nature of the interventions; However, the outcome was objective and thus it is unlikely for lack of blinding to have influenced the results; Group 1 Number missing: 4, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated; Group 2 Number missing: 3, Reason: n=1 dropped out because the treatment made them worse; other reasons not stated	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study (subsidiary papers)	GETSET trial: Clark 2017[164] (Clark 2016[163])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=211)
Countries and setting	Conducted in United Kingdom; Setting: two UK National Health Service (NHS) secondary-care clinics for chronic fatigue syndrome in central London and Kent
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks (8 weeks + 4 weeks)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical diagnosis based on the NICE criteria; medical assessment by the clinic doctor included history, physical, and mental state examinations, and laboratory tests, as recommended by NICE before trial entry to exclude alternative diagnoses.
Stratum	adults; severity mixed or unclear: aged 18 years and older, meeting the NICE criteria
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Aged 18 years and older; diagnosed with chronic fatigue syndrome; meeting the NICE criteria, which are used by NHS clinicians (at least 4 months of clinically evaluated, unexplained, persistent, or relapsing fatigue with a definite onset that has resulted in a substantial reduction in activity and that is characterised by post exertional malaise or fatigue, or both; at least one of ten related symptoms: difficulty sleeping, headaches, cognitive dysfunction, general malaise or flu-like symptoms, painful lymph nodes, sore throat, physical or mental exertion making symptoms worse, dizziness or nausea, palpitations, or multisite muscle or joint pain without evidence of inflammation)
Exclusion criteria	Younger than 18 years; current suicidal thoughts or comorbid psychiatric conditions requiring exclusion; had read the GES guide previously; had already received GET at one of the trial clinics; unable to speak or read English adequately; physical contraindications to exercise

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Recruitment/selection of patients	Adult patients attending study clinics, meeting the eligibility criteria
Age, gender and ethnicity	Age - Mean (SD): GET group 38·1 (11·1) years, control group 38·7 (12·7) years. Gender (M:F): 44/167. Ethnicity: GET group 88% white, control group 90% white
Further population details	-
Indirectness of population	No indirectness: NA
Interventions	(n=107) Intervention 1: Exercise interventions - GET. Graded exercise therapy: Self-help booklet describing a 6-step programme of graded exercise self-management, based on the approach of GET developed for the PACE trial and NICE recommendations. Six steps: stabilising a daily routine, starting regular stretching, deciding on a physical activity goal and choosing a type of activity with which to start, setting a physical activity baseline, increasing the duration of physical activity and finally the intensity. If symptoms increased after an incremental change in activity, participants were advised to maintain activity at the same level until symptoms had settled, before considering another incremental increase. In the first 30 minute session (face-to-face, by Skype or by phone), a physiotherapist provided guidance on following the booklet and answered any questions. Up to 3 further 20 minute appointments by skype/telephone were offered over 8 weeks by 2 experienced physiotherapists who were trained to support participants in using the booklet, but explicitly told not to provide therapy. Physiotherapists inquired about progress, answered questions, with a focus on moving forward to the next step, recognised achievements and provided feedback, with the aim of increasing motivation and self-efficacy. A therapy leader trained the two physiotherapists until they were deemed competent and then provided regular individual supervision. Physiotherapists followed a manual and all participant guidance sessions were audio-recorded for supervision, feedback, and monitoring of treatment integrity. If a participant could not be contacted by telephone or Skype, an email was sent to re-engage them. Duration 8 weeks. Concurrent medication/care: Before randomisation, all patients had at least one specialist medical care consultation, delivered by doctors with specialist experience in chronic fatigue syndrome. SMC could involve prescriptions or advice regarding medication, as indicated for symptoms or comorbid conditions such as insomnia, pain, or depressive illness. Although not routinely scheduled during the trial, further SMC sessions were available after randomisation for patients who required it, but it was not a standardised intervention. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: involved physiotherapists trained by therapy leader (unclear whether

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	they were experienced/specialised in ME/CFS); all participants had access to specialist medical care delivered by doctors with specialist experience in chronic fatigue syndrome (n=104) Intervention 2: usual care - standard medical care. Before randomisation, all patients had at least one specialist medical care consultation, delivered by doctors with specialist experience in chronic fatigue syndrome. SMC could involve prescriptions or advice regarding medication, as indicated for symptoms or comorbid conditions such as insomnia, pain, or depressive illness. Although not routinely scheduled during the trial, further SMC sessions were available after randomisation for patients who required it, but it was not a standardised intervention. Duration study duration. Concurrent medication/care: NA. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: specialist medical care consultation, delivered by doctors with specialist experience in chronic fatigue syndrome
Funding	Academic or government funding (UK National Institute for Health Research, Research for Patient Benefit Programme and the Sue Estermann Fund)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus STANDARD MEDICAL CARE

Protocol outcome 1: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Patient reported clinical global impression of change (positive vs. negative and minimum) at 12 weeks; in CFS symptoms: Group 1 (n=97): 14; Group 2 (n=101): 6; OR; 4.4 (95%CI 1.7 to 12.2) (p value : 0.002); in overall health: Group 1 (n=97): 17; Group 2 (n=101): 5; OR; 4.8 (95%CI 1.9 to 12.4) (p value : 0.001);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 3, Reason: lost to follow up
Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 12 weeks; MD; -4.3 (95%CI -6.3 to -2.4) (p value: <0.0001) Chalder fatigue questionnaire 0-33 Top=High is poor outcome, Comments: Baseline values: GET 26.3 (4.8), control 26 (4.6); adjusted mean difference adjusted for baseline, study centre, high SF36 physical functioning ≥45, and high depression score ≥11.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

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Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical function at 12 weeks; MD; 6.9 (95%CI 2.2 to 11.6) (p value : 0.004) SF36 physical function 0-100 Top=High is good outcome, Comments: Baseline values: GET 47.3 (22.2), control 50.1 (22.6); adjusted mean difference adjusted for baseline, study centre, high SF36 physical functioning ≥45, and high depression score ≥11.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression at 12 weeks; MD; -1.2 (95%CI -1.9 to -0.4) (p value : 0.002) HADS - depression 0-21 Top=High is poor outcome, Comments: Baseline values: GET 9 (3.9), control 8.8 (4.1); adjusted mean difference adjusted for baseline, study centre, high SF36 physical functioning ≥45, and high depression score ≥11.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 3, Reason: lost to follow up

- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety at 12 weeks; MD; -1.1 (95%CI -2 to -0.3) (p value : 0.006) HADS - anxiety 0-21 Top=High is poor outcome, Comments: Baseline values: GET 8.6 (4.7), control 8.7 (4.7); adjusted mean difference adjusted for baseline, study centre, high SF36 physical functioning ≥45, and high depression score ≥11.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 3, Reason: lost to follow up

Protocol outcome 5: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: non-serious adverse events at 12 weeks; Group 1: 27/97, Group 2: 23/101; Comments: not specified
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 3, Reason: lost to follow up

- Actual outcome for adults; severity mixed or unclear: serious adverse events at 12 weeks; Group 1: 1/97, Group 2: 2/101; Comments: a participant

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attended Accident and Emergency [A&E] department after falling and damaging an arm; no fracture was found, and they were discharged; a participant attended A&E after twisting a knee, a damaged cartilage was diagnosed in the knee, and they were discharged; and a participant was admitted to hospital overnight for numbness in the right arm and leg, a neurologist assessed them and they were discharged the next day - unclear which participants belonged to which study group
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 3, Reason: lost to follow up

- Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 12 weeks; Group 1: 0/97, Group 2: 0/101
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 3, Reason: lost to follow up

Protocol outcome 6: Activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: International Physical Activity Questionnaire high vs. low/moderate
at 12 weeks; OR; 3.2 (95%CI 1.8 to 5.8) (p value : <0.0001) , Comments: Baseline results: GET low n=62, moderate n=32, high n=3, control low n=49, moderate n=31, high n=19;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

Protocol outcome 7: Return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and social adjustment scale
at 12 weeks; MD; -1.9 (95%CI -3.7 to -0.2) (p value: 0.033) Work and social adjustment scale 0-40 Top=High is poor outcome, Comments: Baseline values: GET 26 (7.48), control 26.4 (7); adjusted mean difference adjusted for baseline, study centre, high SF36 physical functioning ≥45, and high depression score ≥11.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: control group were more physically active; Group 1 Number missing: 10, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up

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Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Exercise performance measure at longest follow up available

Study	**Guillamo 2016[299]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)

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Countries and setting	Conducted in Spain; Setting: Primary care (exercise physiology unit, School of Medicine, University of Barcelona)
Line of therapy	Unclear
Duration of study	Intervention time: 12 weeks of lab training + 12 weeks of home training
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were diagnosed according to the CDC (1994) criteria; in each case the diagnosis was confirmed by consensus between two physicians
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	not specified
Exclusion criteria	not specified
Recruitment/selection of patients	Patients referred to the Exercise Physiology Unit of the School of Medicine of the University of Barcelona
Age, gender and ethnicity	Age - Mean (range): Active group: 46 (27-64) years; Control group: 47 (28-60) years. Gender (M:F): Randomized: 7/61; Entering programme: 6/49. Ethnicity: not specified
Further population details	-
Extra comments	n=19 (58%) patients entering the intervention group (n=33) also had fibromyalgia; n=32 (97%) also reported pain and mood changes and had some kind of neurocognitive symptoms
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Exercise interventions - GET. Functional reconditioning programme was structured into four microcycles built around the cardiovascular training. These were grouped into a mesocycle, which

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	had to be repeated three times during the complete programme. Each microcycle included five sessions: three of these took place in the laboratory, while the other two were conducted at the patient's home, where they were all allowed two rest days per week. The sessions combined endurance training with the training of other physical capacities such as flexibility (Range of Motion, ROM), muscular strength and skill-related fitness such as balance or coordination. Duration 12 weeks lab training + 12 weeks home training. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: not stated/unclear (n=22) Intervention 2: No treatment. Not specified. Duration not specified. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: Not applicable
Funding	No funding (not stated)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FUNCTIONAL RECONDITIONING PROGRAMME versus NO TREATMENT

Protocol outcome 1: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work (Watts) at 12 weeks post laboratory training; Group 1: mean 93.3 (SD 28.4); n=20, Group 2: mean 85.9 (SD 40.6); n=22; Comments: Maximal workload at maximum effort, assessed through exercise testing at maximum intensity stage.
Risk of bias: All domain - Flawed, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Very high, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Physiological characteristics of the different groups are not specified; Group 1 Number missing: 26, Reason: some declined to participate in the programme; others were excluded because they were already enrolled in another rehabilitation programme or due to other circumstances (e.g. incompatible timetable); reasons for drop-out at monitoring stage were not specified; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: VO2/kg (ml.kg.min) at 12 weeks post laboratory training; Group 1: mean 19.8 (SD 5.4); n=20, Group 2: mean 17.7 (SD 6.2); n=22
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Very high, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Physiological characteristics of the different groups are not specified; Group 1 Number missing: 26, Reason: some declined to participate in the programme; others were excluded because they were already enrolled in another rehabilitation programme or due to other circumstances (e.g. incompatible timetable); reasons for drop-out at monitoring stage were not specified; Group 2 Number missing: 0

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- Actual outcome for adults; severity mixed or unclear: Rate of perceived exertion (RPE) at 12 weeks post laboratory training; Group 1: mean 17.7 (SD 1.7); n=20, Group 2: mean 19.2 (SD 1.1); n=22; Comments: Recorded at rest after the maximal test. Baseline scores: GET 17.8 (SD 1.9); UC 18.0 (4.4). Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Very high, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Physiological characteristics of the different groups are not specified; Group 1 Number missing: 26, Reason: some declined to participate in the programme; others were excluded because they were already enrolled in another rehabilitation programme or due to other circumstances (e.g. incompatible timetable); reasons for drop-out at monitoring stage were not specified; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available

	Hobday 2008[329]
Study	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in United Kingdom; Setting: dedicated chronic fatigue clinic at a large Trust hospital

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Line of therapy	Unclear
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosed according to Fukuda 1994 criteria
Stratum	adults; severity mixed or unclear: age not specified in inclusion criteria, but mean (SD) suggests all adults; diagnosed according to Fukuda 1994 criteria (no further detail on severity)
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients attending or previously attended with a diagnosis of CFS (as specified by Fukuda 1994)
Exclusion criteria	Receiving oral contraceptives, hormone replacement therapy or pregnant; prescribed corticosteroids, immunosuppressive agents, non-steroidal anti-inflammatory agents or antibiotics for 1 month or less before the study; already making significant dietary changes prior to enrolment; taking vitamin and mineral supplements above current recommendations; diagnosed eating disorder
Recruitment/selection of patients	Recruited from a dedicated chronic fatigue clinic at a large Trust hospital; recruitment adverts displayed in patient waiting areas and treatment rooms; local support groups also contacted in effort to publicize the study
Age, gender and ethnicity	Age - Mean (SD): low sugar/yeast diet 44 (10.2) years, healthy eating 42.3 (11.9) years. Gender (M:F): 9/43. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=25) Intervention 1: dietary strategies - exclusion diets / FODMAPS. Low sugar low yeast diet: based on the 'Beat Candida Cook Book', adapted to ensure nutritional requirements were met and that it provided

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	sufficient diversity to promote adherence. All sugar containing foods, refined carbohydrates and yeast containing foods were omitted together with alcohol and caffeine. Fruit and milk consumption were limited and participants were encouraged to have one live yogurt per day. Duration 24 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=27) Intervention 2: dietary strategies - dietary advice. Healthy eating diet: based on Department of Health guidelines for the general population. Participants were encouraged to increase fibre, fruits and vegetables to at least 5 portions per day and reduce consumption of fat and refined carbohydrate. Increasing fish intake to twice per week (1 portion oily) was also recommended. Duration 24 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Other (Nurses, Midwives and Allied Health Research Fund (Barts and the London NHS Trust), The ME Association and Department Nutrition and Dietetics (Barts and the London NHS Trust))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW SUGAR, LOW YEAST DIET versus HEALTHY EATING

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 general health at 24 weeks; Group 1: mean 34.5 (SD 20.3); n=19, Group 2: mean 40.6 (SD 19.4); n=20; SF36 general health 0-100 Top=High is good outcome; Comments: Baseline values: not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 physical function at 24 weeks; Group 1: mean 42.3 (SD 29.2); n=19, Group 2: mean 52.2 (SD 24.1); n=20; SF36 physical function 0-100 Top=High is good outcome; Comments: Baseline values: low sugar/yeast 34.6 (26.6), healthy eating 38.7 (23.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2

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Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 role physical at 24 weeks; Group 1: mean 26.3 (SD 35.8); n=19, Group 2: mean 23.8 (SD 34.9); n=20; SF36 role physical 0-100 Top=High is good outcome; Comments: Baseline values: low sugar/yeast 9 (15.9), healthy eating 11.1 (23.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 role emotion at 24 weeks; Group 1: mean 63.3 (SD 44.5); n=19, Group 2: mean 61.7 (SD 46.3); n=20; SF36 role emotion 0-100 Top=High is good outcome; Comments: Baseline values: low sugar/yeast 55.9 (44.9), healthy eating 55.1 (46.2)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 social function at 24 weeks; Group 1: mean 42 (SD 29.3); n=19, Group 2: mean 50.6 (SD 29.4); n=20; SF36 social function 0-100 Top=High is good outcome; Comments: Low sugar/yeast 38 (26.4), healthy eating 36.1 (25.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 body pain at 24 weeks; Group 1: mean 39.6 (SD 31.2); n=19, Group 2: mean 54.7 (SD 28.7); n=20; SF36 body pain 0-100 Top=High is good outcome; Comments: Baseline values: low sugar/yeast 40.2 (24.5), healthy eating 42.4 (25.1)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 vitality at 24 weeks; Group 1: mean 29.8 (SD 20.7); n=19, Group 2: mean 36.2 (SD 26.4); n=20; SF36 vitality 0-100 Top=High is good outcome; Comments: Baseline values: low sugar/yeast 21.4 (14.5), healthy eating 27 (18.7)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

- Actual outcome for adults; severity mixed or unclear: SF36 mental health at 24 weeks; Group 1: mean 70.7 (SD 21.8); n=19, Group 2: mean 67.8 (SD 18.1); n=20; SF36 mental health 0-100 Top=High is good outcome; Comments: Baseline values: low sugar/yeast 64.2 (17.7), healthy eating 65 (19.2)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue scale at 24 weeks; Group 1: mean 16 (SD 8.2); n=19, Group 2: mean 17.7 (SD 10); n=20; Chalder fatigue scale (14 item) 0-42 Top=High is poor outcome; Comments: Baseline values: low sugar/yeast 23 (5.9), healthy eating 22.5 (6.7)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy

Protocol outcome 3: Psychological status at longest follow up available

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- Actual outcome for adults; severity mixed or unclear: Hospital Anxiety and Depression Scale - anxiety at 24 weeks; Group 1: mean 8.5 (SD 5.2); n=19, Group 2: mean 7.3 (SD 4.1); n=20; HADS anxiety 0-21 Top=High is poor outcome; Comments: Baseline values: low sugar/yeast 9.4 (4.9), healthy eating 8.7 (4.4) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy - Actual outcome for adults; severity mixed or unclear: Hospital Anxiety and Depression Scale - depression at 24 weeks; Group 1: mean 6.5 (SD 3.6); n=19, Group 2: mean 5.4 (SD 3.7); n=20; HADS depression 0-21 Top=High is poor outcome; Comments: Baseline values: low sugar/yeast 8.1 (3.5), healthy eating 7 (3.8) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 6, Reason: 6 were lost to follow up but included in the analysis (unclear whether data were imputed); 2 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy; Group 2 Number missing: 7, Reason: 7 were lost to follow up but included in the analysis (unclear whether data were imputed); 3 received antibiotic therapy, 3 received NSAIDs, 1 received hormone replacement therapy	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study
Huanan 2017[337]

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Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=80)
Countries and setting	Conducted in China; Setting: unclear
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC criteria
Stratum	adults; severity mixed or unclear: age 18-60 years; met CDC 1994 diagnostic criteria
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	aged 18-60 years; met the diagnostic criteria for CFS set by the CDC; provided verbal and written informed consent
Exclusion criteria	cardiovascular, cerebrovascular, liver, kidney, lung, or hematopoietic-system disease; suffering from severe hypertension or diabetes mellitus; with mental disorders; pregnant or breast-feeding; combined thrombocytopenia and coagulation disorders; severely obese.
Recruitment/selection of patients	posters and specialist recommendations in a teaching hospital of a university of TCM
Age, gender and ethnicity	Age - Mean (SD): AT group 41.8 (7.1), 42.63 (6.2) years. Gender (M:F): 46:31. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: PEM not a compulsory feature of CDC 1994 criteria

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Interventions	(n=40) Intervention 1: complementary therapies - traditional Chinese medicine. Abdominal tuina: step one pressing of the abdomen with the palm lasting 5 minutes, step two rotatory kneading of the abdomen lasting 5 minutes, step three pushing and pulling of the abdomen lasting 5 minutes, step four pushing the abdomen with a finger lasting 5 minutes. 20 sessions over 4 weeks - 5 sessions per week. Duration 4 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (n=40) Intervention 2: complementary therapies - acupuncture. Participants lay in the dorsal position. After routine sterilisation, needles 0.25mm x 40mm were inserted in to points at a depth of 50-60mm. After the sensation had been felt by the participant, the uniform reinforcing-reducing method was undertaken. Needles were maintained in this position for 20 minutes. 20 sessions over 4 weeks - 5 sessions per week. Duration 4 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ABDOMINAL TUINA versus ACUPUNCTURE

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue scale 14 at 3 months ; Group 1: mean 7.1 (SD 1.7); n=37, Group 2: mean 8.2 (SD 2); n=35; FS14 0-14 Top=High is poor outcome; Comments: Baseline values: AT 8.9 (1.5), acupuncture 9.3 (1.5)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 3, Reason: lost to follow up (2), other reason (1); Group 2 Number missing: 5, Reason: protocol violation (2), time constraint (2), other reason (1)

Protocol outcome 2: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Self-rating anxiety scale at 3 months ; Group 1: mean 47.7 (SD 3.7); n=37, Group 2: mean 51.3 (SD 5); n=35; Self-rating anxiety scale 20-80 Top=High is poor outcome; Comments: Baseline values: AT 54.6 (3.4), acupuncture 54.2 (3.4)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 3, Reason: lost to follow up (2), other reason (1); Group 2 Number missing: 5, Reason: protocol violation (2), time constraint (2), other reason (1)
- Actual outcome for adults; severity mixed or unclear: Hamilton rating scale for depression at 3 months ; Group 1: mean 6.3 (SD 1.2); n=37, Group 2: mean 7 (SD 1.5); n=35; HAMD not reported Top=High is poor outcome; Comments: Baseline values: AT 11 (2.8), acupuncture 10.9 (2.5)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 3, Reason: lost to follow up (2), other reason (1); Group 2 Number missing: 5, Reason: protocol violation (2), time constraint (2), other reason (1)

Protocol outcome 3: adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Adverse events at 4 weeks ; Group 1: 1/39, Group 2: 2/38; Comments: One patient in the AT group had persistent pain for 1 h during the first treatment and 2 in the acupuncture group had hematoma at the needling site.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up (1); Group 2 Number missing: 2, Reason: protocol violation (2)
- Actual outcome for adults; severity mixed or unclear: Serious adverse events at 4 weeks ; Group 1: 0/39, Group 2: 0/38
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: lost to follow up (1); Group 2 Number missing: 2, Reason: protocol violation (2)

Protocol outcomes not reported by the study	Quality of life at longest follow up available; General symptom scales at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	Janse 2018[354] (Janse 2015[355])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=240)
Countries and setting	Conducted in Netherlands; Setting: Expert Centre for Chronic Fatigue (interventions were internet based)
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: consultants assessed medical status to decide whether referrals had been sufficiently examined to rule out a medical explanation for fatigue; if medical evaluation deemed insufficient then patients seen again for anamnesis, full physical examination, case history evaluation and laboratory tests following national CFS guidelines; psychiatric comorbidity that could explain fatigue ruled out using Mini International Neuropsychiatric Interview
Stratum	adults; severity mixed or unclear: aged 18 years or older; meeting CDC (Fukuda 1994) criteria; score 35 or higher on Checklist Individual Strength fatigue sub scale and 700 or higher on the Sickness Impact Profile 8
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	≥ 18 years; able to speak, read, and write Dutch; able to use a computer and have access to Internet; CFS diagnosis according to the CDC consensus criteria; severe fatigue assessed with the subscale fatigue severity of the Checklist Individual Strength (CIS) operationalized as scoring ≥35; severe disability operationalized as a total score ≥ 700 on the Sickness Impact Profile (SIP8); given written informed consent.
Exclusion criteria	Engaged in a legal procedure concerning disability-related financial benefits; participating in other CFS research.

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Recruitment/selection of patients	consecutive referrals to an Expert Centre for Chronic Fatigue (ECCF), a tertiary treatment centre for chronic fatigue meeting the inclusion criteria
Age, gender and ethnicity	Age - Mean (SD): protocol driven feedback iCBT 36.6 (12.8), feedback on demand iCBT 36.4 (12.4), waiting list 39.9 (12.9). Gender (M:F): 95/145. Ethnicity: not reported
Further population details	
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=80) Intervention 1: Psychological and behavioural interventions - CBT. Web based CBT - protocol driven feedback. Based on face-to-face CBT for CFS protocol and consisting of 7 modules: getting started and goal setting, regulate sleep-wake cycle, helpful beliefs about fatigue, how to communicate with others about fatigue, gradually increasing activities, reaching goals step by step, evaluation and the future. Treatment tailored to patient's current activity pattern, measured by actigraphy. Patients CBT with protocol driven feedback were asked by the therapist to report on their progress according to a schedule set by the therapist (at least fortnightly). Therapists provided feedback and sent reminders if patients did not follow the schedule. The therapists were psychologists trained and experienced in delivering CBT for CFS. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (Based on face-to-face CBT for CFS protocol; therapists were psychologists trained and experienced in delivering CBT for CFS). (n=80) Intervention 2: Psychological and behavioural interventions - CBT. Web based CBT - support on demand. Based on face-to-face CBT for CFS protocol and consisting of 7 modules: getting started and goal setting, regulate sleep-wake cycle, helpful beliefs about fatigue, how to communicate with others about fatigue, gradually increasing activities, reaching goals step by step, evaluation and the future. Treatment tailored to patient's current activity pattern, measured by actigraphy. Patients CBT with support on demand only received feedback if they ask for it. Patients did not receive any reminders from the therapist if they did not report on their progress via email. The therapists were psychologists trained and experienced in delivering CBT for CFS. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No

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	indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (Based on face-to-face CBT for CFS protocol; therapists were psychologists trained and experienced in delivering CBT for CFS). (n=80) Intervention 3: no treatment. Waiting list - started face to face CBT after follow up assessment was complete. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus NO TREATMENT

Protocol outcome 1: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile 8 at 6 months; Group 1: mean 876.4 (SD 664.7); n=160, Group 2: mean 1322.5 (SD 720.8); n=80; Sickness Impact Profile 8 0-5799 Top=High is poor outcome; Comments: Baseline values: CBT 1474 (532.1), waiting list 1607.9 (619.7)

Protocol driven feedback iCBT and feedback on demand iCBT arms combined
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 1, Reason: 1 lost to follow up in each iCBT group; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual strength - fatigue at 6 months; Group 1: mean 36.65 (SD 13.87); n=160, Group 2: mean 43.9 (SD 10.5); n=80; Checklist Individual Strength - fatigue severity sub scale 8-56 Top=High is poor outcome; Comments: Baseline values: CBT 50.3 (5.12), waiting list 49.5 (5.3)

Protocol driven feedback iCBT and feedback on demand iCBT arms combined
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to

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waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 1, Reason: 1 lost to follow up in each iCBT group; Group 2 Number missing: 4, Reason: 4 lost to follow up

- Actual outcome for adults; severity mixed or unclear: Chalder Fatigue Questionnaire at 6 months; Group 1: mean 17.11 (SD 8.071); n=152, Group 2: mean 20.8 (SD 7.3); n=76; Chalder Fatigue Questionnaire 0-33 Top=High is poor outcome; Comments: Baseline values: CBT 23.75 (5.41), waiting list 24.7 (5)
Analysis includes completers only
Protocol driven feedback iCBT and feedback on demand iCBT arms combined
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 4, Reason: 8 across both CBT groups missing, reason unclear; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 6 months; Group 1: mean 75.15 (SD 23.78); n=160, Group 2: mean 70.8 (SD 21); n=80; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 62.65 (19.48), waiting list 62.3 (19.2)
Protocol driven feedback iCBT and feedback on demand iCBT arms combined
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 1, Reason: 1 lost to follow up in each iCBT group; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Symptom Checklist 90 - psychological distress at 6 months; Group 1: mean 137.7 (SD 41.01); n=160, Group 2: mean 154.8 (SD 47.6); n=80; Symptom Checklist 90 - psychological distress 90-450 Top=High is poor outcome; Comments: Baseline values: CBT 154.9 (34.06), waiting list 159.8 (37.7)
Protocol driven feedback iCBT and feedback on demand iCBT arms combined
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to

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waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 1, Reason: 1 lost to follow up in each iCBT group; Group 2 Number missing: 4, Reason: 4 lost to follow up

Protocol outcome 5: adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Adverse events at 6 months; Group 1: 11/77, Group 2: 12/46; Comments: Protocol driven feedback iCBT and feedback on demand iCBT arms combined
CBT: fatigue n=1, pain n=6, distress n=3, other n=1
waiting list: fatigue n=1, pain n=5, distress n=2, other n=4
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 41.5, Reason: 83 across both CBT groups missing; only half of participants asked to report adverse events due to portal update halfway through study; Group 2 Number missing: 34, Reason: only half of participants asked to report adverse events due to portal update halfway through study

Protocol outcome 6: activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Actigraphy mean score at 6 months; Group 1: mean 76.2 unclear (SD 21.42); n=127, Group 2: mean 66.4 unclear (SD 21.5); n=60; Comments: Baseline values: CBT 68.24 (17.75), waiting list 67.6 (18.1)
Analysis based on completers only
Protocol driven feedback iCBT and feedback on demand iCBT arms combined
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 16.5, Reason: 33 across both CBT groups missing, reason unclear; Group 2 Number missing: 20, Reason: reason unclear

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and Social Adjustment Scale at 6 months; Group 1: mean 15.8 (SD 9.87); n=147, Group 2: mean 20.8 (SD 9.2); n=75; Work and Social Adjustment Scale 0-40 Top=High is poor outcome; Comments: Baseline values: CBT 22.9 (11.92), waiting list 23 (6.9)
Analysis includes completers only

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Protocol driven feedback iCBT and feedback on demand iCBT arms combined Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 6 patients were included with <4 CDC symptoms - 1 randomised to waiting list and 5 to on demand iCBT but no differences in other baseline clinical measures; difference between waiting list and on demand iCBT in education level; difference between 2 iCBT arms in unrefreshing sleep; Group 1 Number missing: 6.5, Reason: 13 across both CBT groups missing, reason unclear; Group 2 Number missing: 5, Reason: reason unclear	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; Exercise performance measure at longest follow up available

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Study	Jason 2007[363]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=114)
Countries and setting	Conducted in USA; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: screening questionnaire to assess diagnostic criteria as specified by Fukuda 1994; structured clinical interview for DSM-IV to establish psychiatric diagnoses; physician screening evaluation included an in-depth medical and neurological history and a general and neurological physical examination; relevant medical information gathered to exclude possible other medical causes; laboratory tests included a chemistry screen, complete blood count, ESR, arthritic profile, hep B, Lyme disease screen, HIV screen and urinalysis, tuberculin skin test; detailed medical examination to detect evidence of diffuse adenopathy, hepatosplenomegaly etc.
Stratum	adults; severity mixed or unclear: at least 18 years of age; diagnosed according to Fukuda criteria; people who used wheelchairs, were bedridden or housebound were excluded
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	At least 18 years of age; not pregnant; able to read and speak English; physically capable of attending scheduled sessions
Exclusion criteria	People who used wheelchairs, those who were bedridden or housebound

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Recruitment/selection of patients	Trial information disseminated to medical colleagues through mailings, phone communication and invited grand rounds; study announcements for new participants in local newspapers; recruitment offers at local CFS support groups. Physician referrals (46%), media (34%), other sources (20%).
Age, gender and ethnicity	Age - Other: Mean 43.8 years. Gender (M:F): 19/95. Ethnicity: 87.7 % Caucasian, 4.4% African-American, 4.4% Latino, 3.5 % Asian-American
Further population details	
Extra comments	Participants received $75 for baseline interviews and $75 for 12 month follow up evaluation
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=29) Intervention 1: Psychological and behavioural interventions - CBT. CBT - developed with a member of a team that had completed a successful controlled trial of CBT in CFS; participants asked to evaluate the effect of gradual and consistent increases in activity and utilize strategies other than avoidance. 45 minute meetings once every 2 weeks. Sessions 1-3: engaging participants in therapy and detailed treatment rationale. Sessions 4-7: schedule of planned graded activity developed in collaboration with the participant, where activity and rest were pre-planned and time-contingent rather than symptom driven e.e. 3 x 5 minute walks daily and participants instructed to avoid reducing targets on bad days and exceeding them on good days. Discussion of and assignments related to negative automatic thoughts. Sessions 8-13: Negative automatic thoughts discussed in relation to difficulties and cognitive strategies introduced; encouraged to practice generating less catastrophic and more helpful alternatives, focused on fears, perfectionism, self-criticism and unrealistic performance expectations. Activity gradually increased and rest slowly reduced. A sleep routine was established, including cessation of daytime sleeping, sleep hygiene and stimulus control techniques. Strategies for dealing with setbacks, action plans and coping strategies were created. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: other interventions (delivered by registered nurses with training and experience in psychotherapy; developed with a member of a team that had completed a successful controlled trial of CBT in CFS).

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	(n=29) Intervention 2: Exercise interventions - GET. Anaerobic activity therapy: focused on developing individualized constructive and pleasurable activities accompanied by reinforcement of progress. 45 minute meetings once every 2 weeks. Sessions 1-3: engaging participants in therapy and detailed treatment rationale; treatment plan involved 3 phases - engagement and education, exercise prescription and monitoring and maintaining functional gains. Behavioural goals included energy system education, redefining exercise, prescribing appropriate exercise, increasing daily activities and improving quality of life. Participants shown the principle of specificity in training for achieving functional gains. Informed about importance of gradually increasing anaerobic activity, asked to complete an exercise diary and identify goals/problems regarding exercise compliance. Sessions 4-7: self-monitoring diaries reviewed. Aim of behavioural homework to reinforce gradual consistent increases and discourage rapid fluctuations in activity. Preliminary targets set at safe, achievable level. Individuals given an exercise programme plus flexibility and exercise programme guidelines and an exercise diary. Exercise frequency fixed at 3 times per week. Participants informed that some muscle soreness should be expected and the difference between soreness and pain. Goal to reinforce gradual increases in activity. Sessions 8-13: homework reviewed, problems identified and dealt with, targets set for following week. New targets established after habituation achieved to existing ones. Analysis of activity and symptom records confirmed progress and identified potential and actual setbacks. Behavioural prescriptions with scheduling modifications were developed. Strategies for preventing and dealing with setbacks were rehearsed. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (delivered by an exercise physiologist who had worked on similar interventions). (n=28) Intervention 3: Psychological and behavioural interventions - CBT. Cognitive therapy treatment - cognitive approach focused on developing cognitive strategies to better tolerate and reduce stress and symptoms, to lessen self-criticism and to treat maladaptive beliefs associated with illness-related depression, anxiety and anger. Emphasizes pacing activities - increasing low effort activities and decreasing symptom producing activities. 45 minute meetings once every 2 weeks. Sessions 1-3: Explanation of purpose and goals and rapport building. Personal accounts of illness, including symptoms, effects on vocational functioning, marital satisfaction, social relationships and physical exercise placed in the context of 4 stage progressive model of chronic illness, serving as a coping tool and allowing the therapist to individualize the coping techniques. Sessions 4-8: stress reduction techniques for intrusive symptoms, limitations and emotional distress; relaxation exercises demonstrated and later prescribed for home use; cue-controlled

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	relaxation introduced; cognitive coping statements formulated and prescribed to counteract catastrophic thinking, self-demands and intolerance of symptoms; daily stress and fatigue records reviewed to identify stress/symptom associations. Sessions 9-13: Imagery technique introduced as a method of uplifting mood; if imagery exercises succeeded in elevating mood they were incorporated into daily relaxation practice; quality of social support discussed to identify maladaptive beliefs and used to generate cognitive coping statements, assigned as daily homework to counteract maladaptive thinking about relationships; identification of cognitive difficulties and exposure to memory compensation and cognitive retraining techniques; review of course of therapy; improvements assessed in light of four stage progressive model of CFS; plan developed to maintain effective coping skills. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (formulated and supervised by a clinical psychologist). (n=28) Intervention 4: Relaxation techniques - relaxation techniques (ie Alexander technique). Relaxation treatment - based on prior studies in the area of chronic illness; several types of relaxation demonstrated; 45 minute meetings once every 2 weeks. Sessions 1-3: history obtained and relaxation rationale explained; participants asked to keep a stress/fatigue diary; diaries reviewed and introduction to relaxation; shown how to engage in progressive muscle relaxation and asked to engage in the technique twice daily for the next 2 weeks; results discussed and more coaching provided. Sessions 4-8: relaxation records reviewed; autogenic training introduced and practice sessions devoted to this technique; homework assignments given; breathing focus techniques introduced and participants asked top practice at home. Sessions 9-13: Breathing focus homework reviewed; yoga form stretching introduced and offered in sessio; thematic imagery relaxation introduced and participants asked to practice at home; review of the most helpful techniques and progress made in therapy; post-treatment relaxation programme developed in collaboration with participant. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (supervised by a clinical psychologist).
Funding	Academic or government funding (National Institute of Allergy and Infectious Diseases)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus ANAEROBIC ACTIVITY THERAPY	

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Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of Life Scale at 12 months; Group 1: mean 69.1 (SD 18.99); n=29, Group 2: mean 63 (SD 13.86); n=29; Quality of Life Scale 16-112 Top=High is good outcome; Comments: Baseline values: CBT 66.14 (15.01), anaerobic activity 60.82 (16.43)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Participant Global Impression of Change rating - improved/much improved/very much improved at 12 months; Group 1: 25/29, Group 2: 12/29; Comments: Numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 months; Group 1: mean 5.37 (SD 1.19); n=29, Group 2: mean 5.77 (SD 1.43); n=29; Fatigue Severity Scale 1-7 Top=High is poor outcome; Comments: Baseline values: CBT 6.05 (0.6), anaerobic activity 6.23 (0.85)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 12 months; Group 1: mean 58.64 (SD 30.44); n=29, Group 2: mean 39.72 (SD 27.63); n=29; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 46.36 (27.44), anaerobic activity 39.17 (15.65)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 5: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 12 months; Group 1: mean 13.95 (SD 13.08); n=29, Group 2: mean 16.94 (SD 11.82); n=29; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: CBT 17 (11.3), anaerobic activity 21.11 (11.22)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given
- Actual outcome for adults; severity mixed or unclear: Beck Anxiety Inventory at 12 months; Group 1: mean 11.45 (SD 10.22); n=29, Group 2: mean 12.11 (SD 10.08); n=29; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: CBT 12.09 (7.55), anaerobic activity 12.5 (7.79)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 months; Group 1: mean 3.56 (SD 2.57); n=29, Group 2: mean 3.63 (SD 2.72); n=29; Brief Pain Inventory - severity (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: CBT 4.21 (2.59), anaerobic activity 3.97 (2.29)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

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- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 months; Group 1: mean 4.10 (SD 3.36); n=29, Group 2: mean 3.75 (SD 3.14); n=29; Brief Pain Inventory – interference 0-10 Top=High is poor outcome; Comments: Baseline values: CBT 5.02 (3.36), anaerobic activity 3.77 (3.19), measures the interference of pain in the patient's life. E.g. "During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes)."
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Muscle pain numeric rating scale at 12 months; Group 1: mean 57.50 (SD 32.34)); n=29, Group 2: mean 54.11 (35.50)); n=29; 0-100 Top=High is poor outcome; Comments: Baseline values: CBT 63.75 (27.14), anaerobic activity 56.71 (36.40). 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Joint pain numeric rating scale at 12 months; Group 1: mean 45.53 (SD 42.62); n=29, Group 2: mean 39.74 (SD 41.18)); n=29; 0-100 Top=High is poor outcome; Comments: Baseline values: CBT 55.13 (39.46), anaerobic activity 45.92 (38.16). 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Employment at 12 months; Group 1: 18/29, Group 2: 10/29; Comments: Employment at baseline: CBT 13, anaerobic activity 12
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High,

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Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 8: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 minute walk at 12 months; Group 1: mean 1542.6 meters (SD 634.11); n=29, Group 2: mean 1378.4 meters (SD 208.92); n=29; Comments: Baseline values: CBT 1346.35 (296.76), anaerobic activity 1335.27 (280.99)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus COGNITIVE THERAPY TREATMENT

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of Life Scale at 12 months; Group 1: mean 69.1 (SD 18.99); n=29, Group 2: mean 72.52 (SD 10.84); n=28; Quality of Life Scale 16-112 Top=High is good outcome; Comments: Baseline values: CBT 66.14 (15.01), cognitive therapy 70.24 (14.69)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Participant Global Impression of Change rating - improved/much improved/very much improved at 12 months; Group 1: 25/29, Group 2: 18/28; Comments: Numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not

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different between groups, but no further details on missing data given

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 months; Group 1: mean 5.37 (SD 1.19); n=29, Group 2: mean 5.87 (SD 1.01); n=28; Fatigue Severity Scale 1-7 Top=High is poor outcome; Comments: Baseline values: CBT 6.05 (0.6), cognitive therapy 6.25 (0.6)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 12 months; Group 1: mean 58.64 (SD 30.44); n=29, Group 2: mean 61.09 (SD 23.74); n=28; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 46.36 (27.44), Cognitive therapy 45.65 (23.71)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 5: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 12 months; Group 1: mean 13.95 (SD 13.08); n=29, Group 2: mean 11.86 (SD 7.36); n=28; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: CBT 17 (11.3), cognitive therapy 19.04 (9.36)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Beck Anxiety Inventory at 12 months; Group 1: mean 11.45 (SD 10.22); n=29, Group 2: mean 8.96

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(SD 6.87); n=28; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: CBT 12.09 (7.55), cognitive therapy 10.78 (7.34)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 months; Group 1: mean 3.56 (SD 2.57); n=29, Group 2: mean 3.12 (SD 1.96); n=28; Brief Pain Inventory - severity (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: CBT 4.21 (2.59), cognitive therapy 3.85 (1.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 months; Group 1: mean 4.10 (SD 3.36); n=29, Group 2: mean 3.36 (SD 2.74); n=28; Brief Pain Inventory – interference 0-10 Top=High is poor outcome; Comments: Baseline values: CBT 5.02 (3.36), cognitive therapy 4.02 (2.82), measures the interference of pain in the patient's life. E.g. "During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes)."
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Muscle pain numeric rating scale at 12 months; Group 1: mean 57.50 (SD 32.34)); n=29, Group 2: mean 40.83 (SD 27.92); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: CBT 63.75 (27.14), cognitive therapy 53.61 (33.18); measures the interference of pain in the patient's life; 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but

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baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Joint pain numeric rating scale at 12 months; Group 1: mean 45.53 (SD 42.62); n=29, Group 2: mean 31.52 (SD 30.47); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: CBT 55.13 (39.46), cognitive therapy 51.87 (31.04), measures the interference of pain in the patient's life; 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Employment at 12 months; Group 1: 18/29, Group 2: 16/28; Comments: Employment at baseline: CBT 13, cognitive therapy 14
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 8: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 minute walk at 12 months; Group 1: mean 1542.6 meters (SD 634.11); n=29, Group 2: mean 1513.5 meters (SD 270.95); n=28; Comments: Baseline values: CBT 1346.35 (296.76), cognitive therapy 1389.5 (385.51)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus RELAXATION TREATMENT

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Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of Life Scale at 12 months; Group 1: mean 69.1 (SD 18.99); n=29, Group 2: mean 72 (SD 19.7); n=28; Quality of Life Scale 16-112 Top=High is good outcome; Comments: Baseline values: CBT 66.14 (15.01), relaxation 65.75 (19.32)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Participant Global Impression of Change rating - improved/much improved/very much improved at 12 months; Group 1: 25/29, Group 2: 13/28; Comments: Numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 months; Group 1: mean 5.37 (SD 1.19); n=29, Group 2: mean 5.62 (SD 1.06); n=28; Fatigue Severity Scale 1-7 Top=High is poor outcome; Comments: Baseline values: CBT 6.05 (0.6), relaxation 5.82 (0.74)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 12 months; Group 1: mean 58.64 (SD 30.44); n=29, Group 2: mean 61.2 (SD 27.7); n=28; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 46.36 (27.44), relaxation 53.77 (26.66)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but

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baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 5: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 12 months; Group 1: mean 13.95 (SD 13.08); n=29, Group 2: mean 13.5 (SD 9.97); n=28; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: CBT 17 (11.3), relaxation 17.45 (6.97)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Beck Anxiety Inventory at 12 months; Group 1: mean 11.45 (SD 10.22); n=29, Group 2: mean 11.41 (SD 10.06); n=28; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: CBT 12.09 (7.55), relaxation 14.95 (8.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 months; Group 1: mean 3.56 (SD 2.57); n=29, Group 2: mean 4.6 (SD 2.1); n=28; Brief Pain Inventory - severity (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: CBT 4.21 (2.59), relaxation 4.28 (2.48)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

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- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 months; Group 1: mean 4.10 (SD 3.36); n=29, Group 2: mean 4.44 (SD 2.79); n=28; Brief Pain Inventory – interference 0-10 Top=High is poor outcome; Comments: Baseline values: CBT 5.02 (3.36), relaxation 4.47 (2.76), measures the interference of pain in the patient's life. E.g. "During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes)."
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Muscle pain numeric rating scale at 12 months; Group 1: mean 57.50 (SD 32.34); n=29, Group 2: mean 41.36 (SD 33.85); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: CBT 63.75 (27.14), relaxation 60.52 (26.09), 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Joint pain numeric rating scale at 12 months; Group 1: mean 45.53 (42.62); n=29, Group 2: mean 41.91 (SD 34.73); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: CBT 55.13 (39.46), relaxation 37.62 (37.57), 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Employment at 12 months; Group 1: 18/29, Group 2: 12/28; Comments: Employment at baseline: CBT 13, relaxation 13
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High,

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Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 8: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 minute walk at 12 months; Group 1: mean 1542.6 meters (SD 634.11); n=29, Group 2: mean 1429.33 meters (SD 286.19); n=28; Comments: Baseline values: CBT 1346.35 (296.76), relaxation 1317.78 (296.55)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANAEROBIC ACTIVITY THERAPY versus COGNITIVE THERAPY TREATMENT

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of Life Scale at 12 months; Group 1: mean 63 (SD 13.86); n=29, Group 2: mean 72.52 (SD 10.84); n=28; Quality of Life Scale 16-112 Top=High is good outcome; Comments: Baseline values: anaerobic activity 60.82 (16.43), cognitive therapy 70.24 (14.69)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported, difference in the outcome at baseline; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Participant Global Impression of Change rating - improved/much improved/very much improved at 12 months; Group 1: 12/29, Group 2: 18/28; Comments: Numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and

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not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 months; Group 1: mean 5.77 (SD 1.43); n=29, Group 2: mean 5.87 (SD 1.01); n=28; Fatigue Severity Scale 1-7 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 6.23 (0.85), cognitive therapy 6.25 (0.6)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 12 months; Group 1: mean 39.72 (SD 27.63); n=29, Group 2: mean 61.09 (SD 23.74); n=28; SF36 physical function 0-100 Top=High is good outcome; Comments: Baseline values: Aerobic activity 39.17 (15.65), Cognitive therapy 45.65 (23.71)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 5: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 12 months; Group 1: mean 16.94 (SD 11.82); n=29, Group 2: mean 11.86 (SD 7.36); n=28; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 21.11 (11.22), cognitive therapy 19.04 (9.36)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

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- Actual outcome for adults; severity mixed or unclear: Beck Anxiety Inventory at 12 months; Group 1: mean 12.11 (SD 10.08); n=29, Group 2: mean 8.96 (SD 6.87); n=28; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 12.5 (7.79), cognitive therapy 10.78 (7.34)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 months; Group 1: mean 3.63 (SD 2.72); n=29, Group 2: mean 3.12 (SD 1.96); n=28; Brief Pain Inventory - severity (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 3.97 (2.29), cognitive therapy 3.85 (1.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 months; Group 1: mean 3.75 (SD 3.14); n=29, Group 2: mean 3.36 (SD 2.74); n=28; Brief Pain Inventory – interference 0-10 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 3.77 (3.19), cognitive therapy 4.02 (2.82); measures the interference of pain in the patient's life. E.g. "During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes)."
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Muscle pain numeric rating scale at 12 months; Group 1: mean 54.11 (SD 35.50); n=29, Group 2: mean 40.83 (SD 27.92); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 56.71 (36.40), cognitive therapy 53.61

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(33.18); 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Joint pain numeric rating scale at 12 months; Group 1: mean 39.74 (SD 41.18); n=29, Group 2: mean 31.52 (SD 30.47); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 45.92 (38.16), cognitive therapy 51.87 (31.04); 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Employment at 12 months; Group 1: 10/29, Group 2: 16/28; Comments: Employment at baseline: anaerobic activity 12, cognitive therapy 14
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 8: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 minute walk at 12 months; Group 1: mean 1378.4 meters (SD 208.92); n=29, Group 2: mean 1513.5 meters (SD 270.95); n=28; Comments: Baseline values: anaerobic activity 1335.27 (280.99), cognitive therapy 1389.5 (385.51)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not

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different between groups, but no further details on missing data given

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANAEROBIC ACTIVITY THERAPY versus RELAXATION TREATMENT

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of Life Scale at 12 months; Group 1: mean 63 (SD 13.86); n=29, Group 2: mean 72 (SD 19.7); n=28; Quality of Life Scale 16-112 Top=High is good outcome; Comments: Baseline values: anaerobic activity 60.82 (16.43), relaxation 65.75 (19.32)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Participant Global Impression of Change rating - improved/much improved/very much improved at 12 months; Group 1: 12/29, Group 2: 13/28; Comments: Numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 months; Group 1: mean 5.77 (SD 1.43); n=29, Group 2: mean 5.62 (SD 1.06); n=28; Fatigue Severity Scale 1-7 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 6.23 (0.85), relaxation 5.82 (0.74)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 4: Physical functioning at longest follow up available

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- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 12 months; Group 1: mean 39.72 (SD 27.63); n=29, Group 2: mean 61.2 (SD 27.7); n=28; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: anaerobic activity 39.17 (15.65), relaxation 53.77 (26.66)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported, difference in outcome at baseline; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 5: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 12 months; Group 1: mean 16.94 (SD 11.82); n=29, Group 2: mean 13.5 (SD 9.97); n=28; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 21.11 (11.22), relaxation 17.45 (6.97)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Beck Anxiety Inventory at 12 months; Group 1: mean 12.11 (SD 10.08); n=29, Group 2: mean 11.41 (SD 10.06); n=28; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 12.5 (7.79), relaxation 14.95 (8.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 months; Group 1: mean 3.63 (SD 2.72); n=29, Group 2: mean 4.6 (SD 2.1); n=28; Brief Pain Inventory - severity (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 3.97 (2.29), relaxation 4.28 (2.48)

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 months; Group 1: 3.63 (SD 2.72); n=29, Group 2: mean 4.44 (SD 2.79); n=28; Brief Pain Inventory - interference (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 3.97 (2.29), relaxation 4.47 (2.76); measures the interference of pain in the patient's life. E.g. "During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes)."
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Muscle pain numeric rating scale at 12 months; Group 1: mean 54.11 (SD 35.50); n=29, Group 2: mean 41.36 (SD 33.85); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 56.71 (36.40), relaxation 60.52 (26.09); 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Joint pain numeric rating scale at 12 months; Group 1: mean 39.74 (SD 41.18) n=29, Group 2: mean 41.91 (SD 34.73); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: anaerobic activity 45.92 (38.16), relaxation 37.62 (37.57); 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and

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not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Employment at 12 months; Group 1: 10/29, Group 2: 12/28; Comments: Employment at baseline: anaerobic activity 12, relaxation 13
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 8: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 minute walk at 12 months; Group 1: mean 1378.4 meters (SD 208.92); n=29, Group 2: mean 1429.33 meters (SD 286.19); n=28; Comments: Baseline values: anaerobic activity 1335.27 (280.99), relaxation 1317.78 (296.55)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COGNITIVE THERAPY TREATMENT versus RELAXATION TREATMENT

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of Life Scale at 12 months; Group 1: mean 72.52 (SD 10.84); n=28, Group 2: mean 72 (SD 19.7); n=28; Quality of Life Scale 16-112 Top=High is good outcome; Comments: Baseline values: cognitive therapy 70.24 (14.69), relaxation 65.75 (19.32)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

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Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Participant Global Impression of Change rating - improved/much improved/very much improved at 12 months; Group 1: 18/28, Group 2: 13/28; Comments: Numbers calculated from percentages
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 months; Group 1: mean 5.87 (SD 1.01); n=28, Group 2: mean 5.62 (SD 1.06); n=28; Fatigue Severity Scale 1-7 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 6.25 (0.6), relaxation 5.82 (0.74)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 12 months; Group 1: mean 61.09 (SD 23.74); n=28, Group 2: mean 61.2 (SD 27.7); n=28; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: cognitive therapy 45.65 (23.71), relaxation 53.77 (26.66)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 5: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 12 months; Group 1: mean 11.86 (SD 7.36); n=28, Group 2: mean 13.5 (SD 9.97); n=28; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 19.04 (9.36), relaxation 17.45 (6.97)

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Beck Anxiety Inventory at 12 months; Group 1: mean 8.96 (SD 6.87); n=28, Group 2: mean 11.41 (SD 10.06); n=28; Beck Anxiety Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 10.78 (7.34), relaxation 14.95 (8.94)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported, difference in the outcome at baseline; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 6: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 months; Group 1: mean 3.12 (SD 1.96); n=28, Group 2: mean 4.6 (SD 2.1); n=28; Brief Pain Inventory - severity (VAS) 0-10 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 3.85 (1.94), relaxation 4.28 (2.48)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 months; Group 1: mean 3.36 (SD 2.74); n=28, Group 2: mean 4.44 (SD 2.79); n=28; Brief Pain Inventory – interference 0-10 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 4.02 (2.82), relaxation 4.47 (2.76); measures the interference of pain in the patient's life. E.g. "During the past 24 h pain has interfered with your general activity (0 = does not interfere to 10 = completely interferes)."
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and

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not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Muscle pain numeric rating scale at 12 months; Group 1: mean 40.83 (SD 27.92); n=28, Group 2: mean 41.36 (SD 33.85); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 53.61 (33.18), relaxation 60.52 (26.09); 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

- Actual outcome for adults; severity mixed or unclear: Joint pain numeric rating scale at 12 months; Group 1: mean 31.52 (SD 30.47); n=28, Group 2: mean 41.91 (SD 34.73); n=28; 0-100 Top=High is poor outcome; Comments: Baseline values: cognitive therapy 51.87 (31.04), relaxation 37.62 (37.57); 0 = no problem and 100 = the worst problem possible.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 7: return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Employment at 12 months; Group 1: 16/28, Group 2: 12/28; Comments: Employment at baseline: cognitive therapy 14, relaxation 13
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given

Protocol outcome 8: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 minute walk at 12 months; Group 1: mean 1513.5 meters (SD 270.95); n=28, Group 2: mean 1429.33 meters (SD 286.19); n=28; Comments: Baseline values: cognitive therapy 1389.5 (385.51), relaxation 1317.78 (296.55)

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: 'no statistically significant sociodemographic differences', but baseline demographics and clinical characteristics for each group not reported; Group 1 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given; Group 2 Number missing: , Reason: average dropout rate was 25% and not different between groups, but no further details on missing data given	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Cognitive function at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available

Study	**Jason 2010[361]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: participants' homes
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: diagnosed according to Fukuda 1994 criteria, but unclear how this was assessed
Stratum	adults; severity mixed or unclear: age not part of inclusion criteria but average age suggests participants were adults; diagnosed according to Fukuda 1994 criteria (no further detail on severity reported)
Subgroup analysis within study	Not applicable: NA

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Inclusion criteria	diagnosed with CFS using the Fukuda 1994 criteria and felt they could benefit from having the assistance of a volunteer buddy
Exclusion criteria	not reported
Recruitment/selection of patients	recruited through Chicago area specialists, Chicago support groups, and the Chicago-based CFS newsletter
Age, gender and ethnicity	Age - Other: average age 57.6 years. Gender (M:F): 5/25. Ethnicity: 83.3% were Caucasian and 16.7% were other
Further population details	
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=15) Intervention 1: Psychological and behavioural interventions - buddy or mentor programmes. Student buddies: 15 student buddies with a background in psychology or social work recruited to provide support to their assigned 15 participants. 2 hours per week visiting a participant at their home. Emotional support was provided through offering empathy, trust, listening, understanding, and concern. Any form of direct help provided functional support. Students offer this type of social support by working on a variety of household tasks during their visits such as organizing files, writing letters, creating photo albums, and helping their assigned participants monitor their energy levels. The participants defined the role of the student buddies and their individual needs. This assistance was intended to help participants avoid overexertion, thereby avoiding setbacks and relapses, while increasing their tolerance for activity. Student buddies were required to attend 4 hours of training over a 2-week period and subsequent 1-hour weekly meetings throughout the 4-month duration of the program. Training included theoretical articles on the Envelope Theory, personal stories about people with CFS, empathetic listening training, and role-playing. Student buddies were matched with participants based on the participants' particular needs as well as geographical location of both the student buddy and the participant. and interests that they included on an initial request form. Duration 4 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable

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	(n=15) Intervention 2: no treatment. Control group received no intervention for 4 months after their baseline assessment. After post testing, they were provided a buddy intervention. Duration 4 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (National Institute of Allergy and Infectious Diseases)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUDDY OR MENTOR PROGRAMMES versus NO TREATMENT

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue severity scale at 4 months; Group 1: mean 52.9 (SD 10.5); n=15, Group 2: mean 59.4 (SD 3.7); n=15; Fatigue severity scale 1-63 (not explicitly stated) Top=High is poor outcome; Comments: Baseline values: intervention 59.7 (3.8), control 58 (3.5)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographics or outcome variables; Group 1 Number missing: , Reason: missing data not reported; Group 2 Number missing: , Reason: missing data not reported

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 4 months; Group 1: mean 36.1 (SD 14.1); n=15, Group 2: mean 29.7 (SD 24.9); n=15; SF36 physical function 0-100 Top=High is good outcome; Comments: Baseline values: intervention 31.2 (13.1), control 36 (29.9)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographics or outcome variables; Group 1 Number missing: , Reason: missing data not reported; Group 2 Number missing: , Reason: missing data not reported

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Perceived stress scale at 4 months; Group 1: mean 12.7 (SD 1.8); n=15, Group 2: mean 12.9 (SD 2.1); n=15; Perceived stress scale 0-16 (not explicitly stated) Top=High is poor outcome; Comments: Baseline values: intervention 12.7 (2.1), control 13.6 (2.4)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences between groups in demographics or outcome variables; Group 1 Number missing: , Reason: missing data not reported; Group 2 Number missing: , Reason: missing data not reported

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Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

Study	**Joung 2019[375]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=98)
Countries and setting	Conducted in South Korea; Setting: unclear
Line of therapy	Not applicable
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC criteria
Stratum	adults; severity mixed or unclear: between the ages of 18 and 65 and a diagnosis of CFS, according to the definition of the US Centers for Disease Control and Prevention (CDC)
Subgroup analysis within study	Subgroup: severe (>63 on NRS)

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Inclusion criteria	between the ages of 18 and 65 and a diagnosis of CFS, according to the definition of the US Centers for Disease Control and Prevention (CDC), which requires clinically evaluated, unexplained, persistent, or relapsing chronic fatigue; the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration; sore throat; cervical or axillary lymphadenopathy; muscle pain; multi-joint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours; all other known causes of chronic fatigue must have been ruled out.
Exclusion criteria	participants who required continuous medication for other illnesses or suffered from diseases that induced chronic fatigue within the past 6 months. Such disease include anaemia; liver, kidney, and thyroid dysfunction; depression; and anxiety disorders
Recruitment/selection of patients	recruited from 2 university hospitals
Age, gender and ethnicity	Age - Mean (SD): 39.7 (10.0) years. Gender (M:F): 37/60. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: PEM not an essential feature of the criteria
Interventions	(n=49) Intervention 1: dietary supplementation - pollen extract. Myelophil at a dose of 2 g orally per day. Myelophil is the 1:1 mixture of Astragali Radix and Salviae Miltiorrhizae Radix and was extracted using 30% ethanol for 20 h at 80°C. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=49) Intervention 2: placebo or sham - placebo/sham. Matching placebo containing a starch and lactose mixture of the same size, weight, and shape as Myelophil. Duration 12 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA

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	Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (Traditional Korean Medicine R&D Project, Ministry of Health & Welfare, South Korea and the Ministry of Education, Science and Technology, South Korea)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MYELOPHIL versus PLACEBO/SHAM

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Numeric rating scale at 12 weeks; Group 1: mean 34.8 (SD 16.4); n=48, Group 2: mean 40.53 (SD 19); n=49; numeric rating scale 0-99 Top=High is poor outcome; Comments: Baseline values: myelophil 61.8 (17.4), placebo 62.4 (13.5); numeric rating scale of the Chalder fatigue scale. The questionnaire was translated into Korean and then slightly modified by the NRS method to evaluate the fatigue severity in detail. All participants scored each item on a 10-point scale (0 = not at all to 9 = unbearably severe condition) as a self-rating numeric scale (total score range 0–99).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: dropped out before receiving intervention, so excluded from analysis ; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: Visual analogue scale at 12 weeks; Group 1: mean -3 (SD 2.4); n=48, Group 2: mean -2.5 (SD 2.3); n=49; visual analogue scale 0-10 Top=High is poor outcome; Comments: Baseline values: myelophil 6.9 (1.6), placebo 7.3 (1.9)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: dropped out before receiving intervention, so excluded from analysis ; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Fatigue severity scale at 12 weeks; Group 1: mean -15.3 (SD 14.3); n=48, Group 2: mean -11.1 (SD 11.6); n=49; fatigue severity scale 9-63 Top=High is poor outcome; Comments: Baseline values: myelophil 45.4 (11.8), placebo 45.7 (7.5)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: dropped out before receiving intervention, so excluded from analysis ; Group 2 Number missing: 0

Protocol outcome 2: adverse events at longest follow up available

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- Actual outcome for adults; severity mixed or unclear: adverse events at 12 weeks; Group 1: 7/48, Group 2: 9/49; Comments: Myelophil: diarrhea, knee pain, common cold, migraine, neck pain, pulpitis, cough, anemia. Placebo: vaginitis, finger pain, dyspepsia, fatigue, sore throat, cervical abrasion, shingles, periodontitis, lymphadenopathy, elevated liver enzymes. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: dropped out before receiving intervention, so excluded from analysis ; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: serious adverse events at 12 weeks; Group 1: 0/48, Group 2: 0/49 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: dropped out before receiving intervention, so excluded from analysis ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; General symptom scales at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available; Impact on families/carers at longest follow up available

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Study	Knoop, 2008 trial: Knoop 2008[414]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=171)
Countries and setting	Conducted in Netherlands; Setting: Tertiary care facility
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6-12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 US Centre for Disease Control and Prevention criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years old; spoke and read Dutch; met the 1994 US Center for Disease Control and Prevention criteria for chronic fatigue syndrome; were not engaged in a legal procedure concerning disability-related financial benefits; scored 535 on the Checklist Individual Strength (CIS), fatigue severity sub-scale; had a total score of 4700 on the Sickness Impact Profile–8 (SIP8); and had given written informed consent.
Exclusion criteria	None provided
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (range): CBT/control: 37.6/38.5. Gender (M:F): 35:134. Ethnicity: Unclear
Further population details	

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Extra comments	CBT/control: duration of symptoms 72 months/ 96 months; CIS fatigue severity 49.1; SIP8 total score 1659; SF-36 functional score 52.3
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=85) Intervention 1: Psychological and behavioural interventions - CBT. Guided self-instructions. The intervention consisted of a self-instruction booklet containing information about chronic fatigue syndrome and weekly assignments. The programme took at least 16 weeks, but often more if patients formulated long-term goals such as returning to work. Patients were asked to email (or telephone if they did not have email) at least once every 2 weeks to report their progress. A cognitive–behavioural therapist, trained in regular CBT for chronic fatigue syndrome, responded to this email or call. If patients did not respond every 2 weeks, a reminder was sent by email or patients were telephoned. Duration 16 weeks or more. Concurrent medication/care: After randomization patients placed on a waiting list to await treatment, depending on available treatment capacity. Treatment usually occurred after 6-12 months. Indirectness: Serious indirectness; Indirectness comment: Minimal intervention based on CBT Further details: 1. type of intervention: CFS-specific intervention and cognitive–behavioural therapist, trained in regular CBT for chronic fatigue syndrome, responded to emails and calls (n=86) Intervention 2: no treatment. Waiting list. Duration 6-12 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: Not applicable
Funding	Funding not stated (Declaration of no conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus NO TREATMENT

Protocol outcome 1: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness Impact profile 8 (SIP8) at 6-12 months; MD; -384 (95%CI -543 to -225, Comments: ANCOVA used to adjust for baseline difference.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline details not comprehensive; Group 1 Number missing: 7, Reason: 1= not ME, 6= no explanation; Group 2 Number missing: 5, Reason: 1= not ME, 4= no explanation

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Protocol outcome 2: Fatigue at longest follow up available - Actual outcome for adults; severity mixed or unclear: CIS fatigue severity at 6-12 months; MD; -6.7 (95%CI -9.7 to -3.6, Comments: ANCOVA used to adjust for baseline difference.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline details not comprehensive; Group 1 Number missing: 7, Reason: 1= not ME, 6= no explanation; Group 2 Number missing: 5, Reason: 1= not ME, 4= no explanation Protocol outcome 3: Physical functioning at longest follow up available - Actual outcome for adults; severity mixed or unclear: SF36 physical functioning sub-scale at 6-12 months; MD; 7.5 (95%CI 1.8 to 13.1, Comments: ANCOVA used to adjust for baseline difference.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline details not comprehensive; Group 1 Number missing: 7, Reason: 1= not ME, 6= no explanation; Group 2 Number missing: 5, Reason: 1= not ME, 4= no explanation	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; adverse events at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Kos 2015[419]	Study
Study type	RCT (Patient randomised; Parallel)	Study type
Number of studies (number of participants)	(n=33)	Number of stud
Countries and setting	Conducted in Belgium; Setting: Outpatient clinic	Countries and s
Line of therapy	Unclear	Line of therapy
Duration of study	Intervention + follow up: 5 weeks	Duration of stu
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by an experienced internist, meeting the CDC criteria for CFS (Fukuda 1994) and using serial physical examination and laboratory measurements.	Method of asse condition
Stratum	adults; severity mixed or unclear: Age 18-65; participants had to be able to attend clinic for assessment and treatment which may have excluded those most severely affected - no further info on severity	Stratum
Subgroup analysis within study	Not applicable: NA	Subgroup analy
Inclusion criteria	Adults age 18-65 years; female gender; native Dutch-speaking; diagnosed with CFS, meeting CDC criteria	Inclusion criteri
Exclusion criteria	Treated with activity pacing or CBT before or had already entered the MDT program for CFS at their local hospital	Exclusion criteri
Recruitment/selection of patients	Participants were recruited from a waiting list for MDT rehabilitation	
Age, gender and ethnicity	Age - Mean (SD): Activity pacing group 39.3 (11.4) years; relaxation group 40.8 (11.1) years. Gender (M:F): 0/33. Ethnicity: Not reported	Recruitment/se
Further population details	-	

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Extra comments	-	Age, gender and
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.	
Interventions	(n=16) Intervention 1: self-management - adaptive pacing therapy. 3 one-on-one sessions with an occupational therapist, weekly for 3 consecutive weeks. Activity pacing self-management (APSM) program consisted of a stabilisation phase and a grading phase. Stabilisation phase focused on coaching participants how to perform daily life activities (all responsibilities and desired activities in the areas of personal and childcare, domestic care, productivity, and leisure) within the limits of their actual capacity. Participants estimated their current physical and mental capabilities before commencing an activity, keeping in mind the fluctuating nature of their symptoms. The activity duration used in the program was 25-50% lower than the capacity participants reported to account for any overestimations. Each activity block was interspersed with breaks (resting or performing a different type of light activity) equal to the duration of the activity. Participants received education on factors influencing fatigue and strategies to cope with fatigue and pace activities. Participants kept a diary of all activities and duration for 7 days to increase their awareness and guide implementation of coping strategies. Grading phase, where activity levels were increased gradually, was commenced once participants were able to control daily life activities without excessive fatigue. At sessions participants set/adjusted goals (prioritized based on activities reported in COPM and participants diary) and performed in real life in between sessions. Duration 3 weeks. Concurrent medication/care: Participants were asked not to change or initiate any pharmaceutical intervention during the study period. None of the participants reported initiating or altering other treatments during study period, except for one dropout who had to undergo surgery. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (Sessions delivered by occupational therapist, unclear if CFS experience. Intervention was designed to take into account fluctuating symptoms of CFS and overestimations of ability). (n=17) Intervention 2: Relaxation techniques - relaxation techniques (ie Alexander technique). 3 one-on-one sessions with a physiotherapist, lasting 60-90 mins each, weekly for 3 consecutive weeks. Relaxation therapy comprised of education about the role of stress in CFS biology, and the opportunities stress management provides to handle this issue. Patients were then taught how to apply stress management techniques like Jacobson relaxation skills, Schultz relaxation skills, visualization, and other techniques. Participants completed a stress reaction diary during the session, and the therapist provided the participant with	Further populat Indirectness of Interventions Funding RESULTS (NUM Protocol outcor - Actual outcom 19.4); n=20; SF3 Risk of bias: All Crossover - Low

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	activities to improve coping in similar future stress events. Duration 3 weeks. Concurrent medication/care: Participants were asked not to change or initiate any pharmaceutical intervention during the study period. None of the participants reported initiating or altering other treatments during study period. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (Sessions delivered by a physical therapist, unclear if CFS experience. Education on role of stress in CFS given as part of intervention).	the analysis (un Number missing received NSAID - Actual outcom 24.1); n=20; SF3 Risk of bias: All Crossover - Low the analysis (un Number missing received NSAID - Actual outcom 34.9); n=20; SF3 Risk of bias: All Crossover - Low the analysis (un Number missing received NSAID - Actual outcom 46.3); n=20; SF3 Risk of bias: All Crossover - Low the analysis (un Number missing received NSAID - Actual outcom n=20; SF36 soci
Funding	Academic or government funding (Research council of Artesis Plantijn University College, Antwerp)	
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACTIVITY PACING versus RELAXATION THERAPY Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: SF-36 physical functioning at 5 weeks; Group 1: mean 53.2 (SD 20.9); n=12, Group 2: mean 45 (SD 12.7); n=14; Comments: Baseline scores (SD): pacing group 46.3 (21.9); relaxation group 41.2 (19.0) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate) - Actual outcome for adults; severity mixed or unclear: SF-36 role-physical at 5 weeks; Group 1: mean 36.4 (SD 39.3); n=12, Group 2: mean 11.5 (SD 28.2); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 12.5 (27.4); relaxation group 4.4 (9.8) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female). Duration of illness not reported. Difference in baseline score of 8.1 points; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate) - Actual outcome for adults; severity mixed or unclear: SF-36 bodily pain at 5 weeks; Group 1: mean 48 (SD 24.8); n=12, Group 2: mean 40.4 (SD 15.5); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 45.1 (21.1); relaxation group 40.3 (17.5) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all	

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participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)

- Actual outcome for adults; severity mixed or unclear: SF-36 general health at 5 weeks; Group 1: mean 42.5 (SD 19); n=12, Group 2: mean 39 (SD 20.1); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 35.2 (19.4); relaxation group 35.4 (23.2)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)

- Actual outcome for adults; severity mixed or unclear: SF-36 vitality at 5 weeks; Group 1: mean 38.6 (SD 14); n=12, Group 2: mean 35 (SD 15.3); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 29.1 (11.4); relaxation group 30.0 (12.2)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)

- Actual outcome for adults; severity mixed or unclear: SF-36 social functioning at 5 weeks; Group 1: mean 53.4 (SD 19.4); n=12, Group 2: mean 43.1 (SD 21.7); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 43.2 (18.0); relaxation group 37.5 (21.7)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)

- Actual outcome for adults; severity mixed or unclear: SF-36 role-emotional at 5 weeks; Group 1: mean 93.9 (SD 20.1); n=12, Group 2: mean 51.3 (SD 46.4); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 72.7 (32.8); relaxation group 66.7 (38.5)
Effect size between groups (cohen's d [95% CI]): 1.21 [0.3 to 1.9]
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover

Risk of bias: All
Crossover - Low
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- Actual outcom
n=20; SF36 vital
Risk of bias: All
Crossover - Low
the analysis (un
Number missing
received NSAID

- Actual outcom
18.1); n=20; SF3
Risk of bias: All
Crossover - Low
the analysis (un
Number missing
received NSAID

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- Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)

- Actual outcome for adults; severity mixed or unclear: SF-36 mental health at 5 weeks; Group 1: mean 69.5 (SD 10.6); n=12, Group 2: mean 58.2 (SD 21.9); n=14; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 63.3 (11.1); relaxation group 57.8 (23.4)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)

Protocol outcome 2: General symptom scales longest follow up available (Outcome not analysed as median only)
- Actual outcome for adults; severity mixed or unclear: CFS symptom list - total score at 5 weeks; CFS symptom list 0-100 Top=High is poor outcome; Follow-up scores, median (IQR): pacing group 55.1 (28.9); relaxation group 44 (43.2)
Baseline scores, median (IQR): pacing group 53.9 (26.7); relaxation group 58.8 (28.7)
The CFS symptom list is a self-report instrument to assess symptom severity in CFS. The severity of 19 frequently reported symptoms such as pain, fatigue, attention disorders, muscle weakness are scored on a visual analogue scale. The total score is the mean of all 19 severity scores;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)Protocol outcome 3: Fatigue at longest follow up available (Outcome not analysed as median only)

- Actual outcome for adults; severity mixed or unclear: Checklist individual strength - total score at 5 weeks; Follow-up scores, median (IQR): pacing group 91 (18.0); relaxation group 107 (26.5)
Baseline scores, median (IQR): pacing group 112 (15.5); relaxation group 120 (10.5);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number

Protocol outcor
- Actual outcom
n=20; Chalder fa
Risk of bias: All
Crossover - Low
the analysis (un
Number missing
received NSAID

Protocol outcor
- Actual outcom
Group 2: mean
(4.4)
Risk of bias: All
Crossover - Low
the analysis (un
Number missing
received NSAID

- Actual outcom
n=19, Group 2:
eating 7 (3.8)
Risk of bias: All
Crossover - Low
the analysis (un
Number missing
received NSAID

Protocol outcor
study

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missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate) Protocol outcome 4: Physical functioning at longest follow up available - Actual outcome for adults; severity mixed or unclear: Canadian occupational performance measure - performance at 5 weeks; Group 1: mean 5.6 (SD 1.4); n=12, Group 2: mean 5.1 (SD 1.5); n=14; Canadian occupational performance measure 1-10 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 4.1 (1.5); relaxation group 4.8 (1.4) 'Effect size' between groups (cohen's d [95% CI]); 0.34 [-0.2 to 0.9] Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate) - Actual outcome for adults; severity mixed or unclear: Canadian occupational performance measure - satisfaction at 5 weeks; Group 1: mean 5.7 (SD 1.9); n=12, Group 2: mean 4.5 (SD 1.5); n=14; Canadian occupational performance measure 1-10 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 3.9 (2.1); relaxation group 4.3 (1.8) Effect size between groups (cohen's d [95% CI]); 0.74 [0.1 to 1.4] Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender (all participants female), baseline score comparable. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 4, Reason: n=1 did not receive intervention due to surgery; n=3 lost to follow-up (no longer willing to participate); Group 2 Number missing: 3, Reason: n=3 did not receive intervention (no longer willing to participate)	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

Study
Study type
Number of stud
Countries and s
Line of therapy
Duration of stu
Method of asse
Stratum
Subgroup analy
Inclusion criteri
Exclusion criteri

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Study	Lopez, 2011 trial: Lopez 2011[465]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in USA; Setting:
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 CDC and physical exam
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	CFS diagnosis by 1994 CDC criteria and physical exam; aged 18-60; 8th grade education or higher; fluent in English
Exclusion criteria	Exclusionary diagnoses; positive for Lyme disease; infection treated with antibiotics in previous 3 weeks; GA for surgery in past month; on any immunomodulatory drugs; history of major psychiatric illness; currently in psychotherapy; substance or drug abuse; major psychiatric illness
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 45.9 (9.3). Gender (M:F): 11.6: 88.4. Ethnicity: Caucasian 76.8%; Latino 17.4%; Caribbean Islander 1.4%; Biracial 1.4%; another ethnic group 2.9%
Further population details	-

Recruitment/se
Age, gender and
Further populat
Indirectness of
Interventions
Funding

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Extra comments	Perceived stress 27.99; overall quality of life (QOLI) 3.18; QOLI raw score 0.68; QOLI T score 67; POMS - total mood disturbance 40.46	RESULTS (NUMI
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.	Protocol outcor
Interventions	(n=44) Intervention 1: Psychological and behavioural interventions - CBT. Cognitive behavioural stress management. The CBSM intervention (14) consisted of 12 weekly group meetings held in 2-hour sessions. Each 2-hour session consisted of two parts: a relaxation component lasting from 20–30 minutes, and a didactic and discussion component that lasted 90 minutes. During the relaxation component, participants were instructed in specific relaxation techniques, including progressive muscle relaxation and visualization techniques. During this 20– 30 min period, participants discussed their views on the helpfulness of the techniques, as well as any barriers to practice, and the progress of their at-home practice. During the 90-min didactic component, participants were taught to better recognize how stress impacts them emotionally and physically, and the relationship between thoughts, feelings, and behaviours. The primary therapeutic technique used was cognitive restructuring targeting cognitive appraisals of ongoing stressors. In contrast to previously studied CBT techniques that target CFS-specific cognitions and physical de-conditioning behaviours, a specific focus of CBSM is on teaching participants general stress management skills that they can apply to ongoing life events as well as CFS-specific stressors (26).In addition to cognitive restructuring, they also learned specific coping skills and interpersonal communication skills such as assertiveness and anger management, which are designed to better attract, utilize and maintain social support, an important stress moderator. Homework pertaining to session topics was assigned each week and was collected and discussed in the subsequent week. Home practice of relaxation techniques was also encouraged. The CBSM groups were led by a post-doctoral clinical fellow and advanced psychology graduate students. Duration 12 weeks. Concurrent medication/care: Participants in both conditions were given a workbook and three relaxation tapes to practice at home. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: not stated/unclear (n=25) Intervention 2: placebo or sham - placebo/sham. Psycho-education seminar control group. The half-day PE condition summarized many of the strategies from the 12 week CBSM group but in a condensed format. The seminar was scheduled during the 6th week of the CBSM group and was run by a clinical post-doctoral fellow. Duration 0.5 days. Concurrent medication/care: Participants in both conditions were given a workbook and three relaxation tapes to practice at home. Indirectness: No indirectness	- Actual outcom FS14 0-14 Top= Risk of bias: All - Low; Indirectn Number missing Protocol outcor - Actual outcom 5); n=35; Self-r Risk of bias: All - Low; Indirectn Number missing - Actual outcom mean 7 (SD 1.5 Risk of bias: All - Low; Indirectn Number missing Protocol outcor - Actual outcom had persistent p Risk of bias: All - Low; Indirectn Reason: protoc - Actual outcom Risk of bias: All - Low; Indirectn

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	Further details: 1. type of intervention: not stated/unclear (run by a clinical post-doctoral fellow, but unclear whether they were experienced/specialised in ME/CFS)	Reason: protoco
Funding	Academic or government funding (National Institutes of Health funding)	Protocol outcor
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus PSYCHOEDUCATION SEMINAR CONTROL GROUP Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: Quality of Life Inventory (QOLI) raw score at 12 weeks; Group 1: mean 1.17 (SD 1.83); n=38, Group 2: mean 0.82 (SD 1.37); n=20; Quality of life inventory unclear Top=High is good outcome; Comments: Group x time interaction: F=4.0, p=0.05, favouring CBSM. Baseline scores mean (sd): CBSM 0.85 (1.88), Control 1.12(1.46) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differences in some outcome measures at baseline suggest randomisation did not create comparable groups; Group 1 Number missing: 6, Reason: reasons not given; Group 2 Number missing: 5, Reason: reasons not given Protocol outcome 2: General symptom scales longest follow up available - Actual outcome for adults; severity mixed or unclear: CDC Symptom Inventory at 12 weeks; Group 1: mean 2.01 (SD 0.33); n=38, Group 2: mean 2.08 (SD 0.39); n=20; CDC symptom inventory not reported Top=High is poor outcome; Comments: Group x time interaction: F=4.32, p=0.04, favouring CBSM Baseline scores mean (sd): CBSM 2.07 (0.38), Control 1.96 (0.32) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differences in some outcome measures at baseline suggest randomisation did not create comparable groups; Group 1 Number missing: 6, Reason: reasons not given; Group 2 Number missing: 5, Reason: reasons not given Protocol outcome 3: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Perceived Stress Scale at 12 weeks; Group 1: mean 27.11 (SD 10.05); n=38, Group 2: mean 23.46 (SD 6.72); n=20; Perceived stress scale 0-40 Top=High is poor outcome; Comments: Group x time interaction (groups differed at baseline): F=5.07, p=0.03, favouring CBSM Baseline scores mean (sd): CBSM 29.22 (8.77), Control 22.39 (7.31) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differences between outcomes at baseline suggest randomisation did not create comparable groups; Group 1 Number missing: 6, Reason: reasons not given; Group 2 Number missing: 5, Reason: reasons not given		

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- Actual outcome for adults; severity mixed or unclear: Profile of Mood States (POMS) - total mood disturbance at 12 weeks; Group 1: mean 34.03 (SD 34.43); n=38, Group 2: mean 27.35 (SD 21.61); n=20; Profile of mood states not reported Top=High is poor outcome; Comments: Group x time interaction (groups differed at baseline): F=4.12, p=0.05, favouring CBSM Baseline scores mean (sd): CBSM 44.01 (32.85), Control 21.62 (26.32) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Large differences in outcome at baseline suggest randomisation did not create comparable groups; Group 1 Number missing: 6, Reason: reasons not given; Group 2 Number missing: 5, Reason: reasons not given	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	McDermott 2006[492]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=71)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient
Line of therapy	Unclear
Duration of study	Other: 10 weeks (2 weeks pre-randomisation assessment, 8 weeks treatment and follow-up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants had a diagnosis of CFS according to the CDC criteria, recruited from specialist CFS clinic.
Stratum	adults; severity mixed or unclear: Adults >18 years; no info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Adults age >18 years; diagnosis of CFS according to 1994 CDC criteria; illness duration between 6-60 months; 2 or more of the following symptoms suggestive of lymph node activation: tender lymph nodes, sore throat, poor temperature control.
Exclusion criteria	Taking immudomodulatory medications; serious illness other than CFS; unable to attend outpatient appointments; pregnant or breastfeeding.
Recruitment/selection of patients	Participants were recruited from outpatients attending a specialist CFS rehabilitation service. Potential participants identified by database searching of existing CFS service patients and by screening all new patients referred to the clinic for eligibility.
Age, gender and ethnicity	Age - Mean (SD): biobran group: 43 (12) years; placebo group: 42 (15) years. Gender (M:F): 20/51. Ethnicity:

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Further population details	-
Indirectness of population	Very serious population indirectness: Study included only a subset of CFS population with symptoms suggestive of immune activation (≥2 of: tender lymph nodes, sore throat or poor temperature control) and 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=37) Intervention 1: dietary supplementation - magnesium. 2000mg sachets of Biobran MGN-3, each containing 1000mg of active ingredient and 1000mg of excipient (500mg microcrystalline cellulose, 260mg corn starch, 200mg dextrin, 40mg tricalcium phosphate). Identical to over the counter preparation sold in UK and USA. The active ingredient is arabinoxylane, a hemicellulose compound released from rice bran when it is incubated with an enzyme from the shitake mushroom. Defined by MHRA as a food supplement. Patients were asked to take a dose of 2g three times per day dissolved in water or milk for 8 weeks. Duration 8 weeks. Concurrent medication/care: All patients attending the outpatient service are advised to maintain a natural healthy diet with adequate intake of fruit and vegetables. No additional instructions on diet were given to participants and food intake was not monitored. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=34) Intervention 2: placebo or sham - placebo/sham. Study packs containing placebo were identical to those containing Biobran in every way other than the study number marked on the outside. The contents of the placebo were indistinguishable in taste and appearance from the Biobran sachets. The study team evaluated both placebo and Biobran to confirm equivalence. Patients were asked to take a dose of 2g three times per day dissolved in water or milk for 8 weeks. Duration 8 weeks. Concurrent medication/care: All patients attending the outpatient service are advised to maintain a natural healthy diet with adequate intake of fruit and vegetables. No additional instructions on diet were given to participants and food intake was not monitored. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Study funded by industry (Daiwa Pharmaceutical Company)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BIOBRAN versus PLACEBO	

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Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Patient global impression of change (PGIC) at 8 weeks; Group 1: 4/34, Group 2: 4/30; Comments: Events represent participants who felt they were 'much better' (no participants felt 'very much better').
Participants rated overall change in their condition on a 7 point scale ranging from 'very much better' to 'very much worse'. Participants defined as improved by the PGIC were those that gave a rating of 'much better' or 'very much better'.
No baseline measurement
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation similar; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

- Actual outcome for adults; severity mixed or unclear: WHOQOL-BREF - physical wellbeing subscale at 8 weeks; Group 1: mean 3.1 (SD 14.6); n=34, Group 2: mean 5 (SD 15.2); n=30; WHOQOL-BREF 0-100 Top=High is good outcome; Comments: MD (95% CI): 1.9 (-5.7, 9.4) p value 0.62 (positive change scores indicate improvement)
Baseline scores: biobran 37.7 (16.1); placebo 35.6 (15.6)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

- Actual outcome for adults; severity mixed or unclear: WHOQOL-BREF - psychological wellbeing subscale at 8 weeks; Group 1: mean 1.4 (SD 9.8); n=34, Group 2: mean -1 (SD 12.9); n=30; WHOQOL-BREF 0-100 Top=High is good outcome; Comments: MD (95% CI): -2.4 (-8.2, 3.4) p value 0.41 (positive change scores indicate improvement)
Baseline scores: biobran 48.4 (14.3); placebo 45.2 (18.1)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

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- Actual outcome for adults; severity mixed or unclear: WHOQOL-BREF - social wellbeing subscale at 8 weeks; Group 1: mean -1.3 (SD 12.7); n=34, Group 2: mean 6.9 (SD 14); n=30; WHOQOL-BREF 0-100 Top=High is good outcome; Comments: MD (95% CI): 8.2 (1.5, 14.9) p value 0.02 (positive change scores indicate improvement)
Baseline scores: biobran 60.3 (21.0); placebo 53.9 (22.2)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

- Actual outcome for adults; severity mixed or unclear: WHOQOL-BREF - environmental wellbeing subscale at 8 weeks; Group 1: mean -0.6 (SD 10); n=34, Group 2: mean 1.6 (SD 10.7); n=30; WHOQOL-BREF 0-100 Top=High is good outcome; Comments: MD (95% CI): 2.2 (-3.1, 7.5) p value 0.41 (positive change scores indicate improvement)
Baseline scores: biobran 68.0 (14.2); placebo 61.4 (18.1)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Measure yourself medical outcomes profile 2 (MYMOP 2) - total score at 8 weeks; Group 1: mean -0.1 (SD 1.6); n=34, Group 2: mean -0.5 (SD 1.2); n=30; Measure yourself medical outcomes profile 2 0-6 Top=High is poor outcome; Comments: Baseline scores not reported. Negative change scores indicate improvement.
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation. Baseline scores are not reported; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder's fatigue scale - total score at 8 weeks; Group 1: mean -1.1 (SD 4.4); n=34, Group 2: mean -

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1.4 (SD 3.8); n=30; Chalder's fatigue scale (11-item) 0-11 (bimodal scoring) Top=High is poor outcome; Comments: MD (95% CI): -0.2 (-2.3, 1.8) p value 0.81 (negative change scores indicate improvement)
Baseline scores: Biobran 8.5 (3.5); placebo 7.7 (3.9)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety subscale at 8 weeks; Group 1: mean -1 (SD 5.9); n=34, Group 2: mean -0.1 (SD 2.2); n=30; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: MD (95% CI): 0.8 (-0.3, 2.0) p value 0.15 (negative change score indicates improvement)
Baseline scores: Biobran 10.9 (4.6); placebo 10.2 (4.4)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression subscale at 8 weeks; Group 1: mean -0.4 (SD 2.9); n=34, Group 2: mean -1 (SD 1.8); n=30; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: MD (95% CI): -0.6 (-1.8, 0.7) p value 0.35 (negative change score indicates improvement)
Baseline scores: Biobran 8.9 (3.6); placebo 9.7 (5.2)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation, baseline scores comparable; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear

Protocol outcome 5: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Serious adverse events at 8 weeks; Group 1: 0/37, Group 2: 0/34

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Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation comparable. ; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study.; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear - Actual outcome for adults; severity mixed or unclear: Minor side effects leading to discontinuation at 8 weeks; Group 1: 3/37, Group 2: 1/34; Comments: Biobran group: n=1 mild nausea; n=1 exacerbation of CFS symptoms; n=1 exacerbation of irritable bowel symptoms Placebo group: n=1 exacerbation of fatigue and anxiety. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, symptoms suggestive of immune activation comparable. ; Blinding details: Identical placebo/active treatment. Researchers/participants/database manager/statistician remained blinded until analysis completed. 68% of patients guessed that they were in placebo group at end of study.; Group 1 Number missing: 3, Reason: Unclear; Group 2 Number missing: 4, Reason: Unclear	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Moss-Morris 2005[521]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in New Zealand; Setting: Specialist 'CFS' private general practice
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 week intervention; 42 weeks post baseline assessment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: patients met CDC criteria for CFS as assessed by specialist general practitioner and labelled themselves as such
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients meeting the US CDC criteria for CFS, that were between 18 and 65 years of age
Exclusion criteria	Patients unable to undergo exercise testing for medical reasons or who were already performing a consistent and regular exercise programme
Recruitment/selection of patients	Volunteer patients from a specialist CFS private general practice in Auckland advertising that the University of Auckland was running a graded exercise study
Age, gender and ethnicity	Age - Mean (SD): 40.9 years; experimental group: 36.72 (11.83), control group: 45.48 (10.45). Gender (M:F): 15/34. Ethnicity: Not specified
Further population details	-

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Extra comments	Ages ranged from 19 to 60 years; median duration of illness was 3.08 years, ranging from 6 months to 45 years; 22.4% were unemployed or unable to work due to disability; 56% were either possible or probable cases of psychiatric disorder (30% being possible or probable cases of depression; 42% being possible or probable cases of anxiety disorder) as assessed by the HADS anxiety and depression sub-scales.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=25) Intervention 1: Exercise interventions - GET. An individual plan for starting the exercise program was developed; the target heart rate for each participant was initially set at 40% of VO2max (approximately 50% max HR) attained on the treadmill test, to be maintained for 10-15 minutes 4 to 5 times a week; exercise goals were set collaboratively between the researcher and participant. Initial exercise intensity and duration were set at a level that had been identified during exercise testing as achievable and unlikely to exacerbate symptoms in the patient. participants were issued with a polar heart rate monitor to assess heart rate during exercise sessions, which assisted participants to meet but not to exceed the prescribed intensity levels and provided external monitoring which reduced the likelihood of focusing on and adjusting exercise intensity in response to bodily symptoms. Researchers and participants met weekly over a period of 12 weeks to assess progress, provide encouragement and set new exercise goals. During the first six weeks increases focused on duration of exercise and involved duration increases of 3-5 minutes per week. After six weeks, intensity of exercise was gradually increased aiming for heart rate increases of approximately 5 beats/minute per week. The final goal was for each participant to be exercising for approximately 30 minutes for 5 days a week at intensity level relating to 80 % of expected maximum heart rate (70% of VO2max). . Duration 12 weeks. Concurrent medication/care: standard medical care (details not specified). Indirectness: No indirectness Further details: 1. type of intervention: not stated/unclear (n=24) Intervention 2: usual care - standard medical care. Standard medical care was provided by a 'CFS' specialist physician. Duration not specified. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: Provided by a ‘CFS’ specialist physician
Funding	Academic or government funding (Study supported in part by two University of Auckland Staff Grants)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GRADED EXERCISE THERAPY versus STANDARD MEDICAL CARE

Protocol outcome 1: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical global impression scale at 42 weeks after baseline assessment (6 months); Group 1: 9/16, Group 2: 5/17; Comments: Number of events calculated from percentage of people self-reported to have clinically improved ('much better' and 'very much better' were classed as improvement, and other responses classed as no improvement. Participants were asked to respond to the question 'how would you rate the change in you CFS in the last 3 months?' by indicating their response from seven possible scores ranging from 'very much worse' to 'very much better'
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline between group differences in age, length of illness and gender. These are reported not to correlate significantly with the outcome; Group 1 Number missing: 9, Reason: n=3 had dropped out of treatment (one had to return home to the United States, one injured his calf and decided not to continue, one could not be contacted at the time of follow-up); n=6 did not return questionnaires at 6 months; Group 2 Number missing: 7, Reason: n=3 did not return follow-up questionnaires at 12 weeks; n=4 did not return questionnaires at 6 months

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Total fatigue at 12 weeks; Group 1: mean 13.91 (SD 10.88); n=22, Group 2: mean 24.41 (SD 9.69); n=21; Chalder fatigue scale (14 item; 0, 1, 2, 3 scoring system) 0-42 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline between group differences in age, length of illness and gender. These are reported not to correlate significantly with the outcome; Group 1 Number missing: 3, Reason: dropped out of treatment (one had to return home to the United States, one injured his calf and decided not to continue, one could not be contacted at the time of follow-up); Group 2 Number missing: 3, Reason: did not return follow-up questionnaires

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 Physical functioning at 12 weeks; Group 1: mean 69.05 (SD 21.94); n=22, Group 2: mean 55 (SD 22.94); n=21; SF-36 Physical functioning 0-100 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline between group differences in age, length of illness and gender; age reported to correlate significantly with the outcome and controlled for in the regression analysis testing for group differences. There is also a difference of 7.45 points in baseline scores for this outcome; Group 1 Number missing: 3, Reason: dropped out of treatment (one had to return home to the United States, one injured his calf and decided not to continue, one could not be contacted at the time of follow-up);

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Group 2 Number missing: 3, Reason: did not return follow-up questionnaires Protocol outcome 4: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: VO2 peak (ml/kg/min) at 12 weeks; Group 1: mean 27.21 (SD 5.53); n=14, Group 2: mean 25.8 (SD 3.95); n=12; Comments: Participants underwent incremental exercise testing to determine maximum aerobic capacity (VO2 peak) on a motorized treadmill. Following a brief warm-up on the treadmill, the walking protocol began at an initial intensity of 4 metabolic equivalents (METS; 1 MET equalling resting energy expenditure) and increased 1 MET every 2 minutes until maximal effort was achieved. Participants wore a polar heart rate monitor during the test, and HR was recorded every 30 seconds. Due to the fact that few participants were capable of achieving their age predicted maximal heart rate or a plateau in oxygen consumption at peak workload, the study reports it was not possible to achieve a true physiological VO2 max. Instead VO2 peak, which measures the highest single oxygen consumption measurement, was used. While this measure underestimates the subjects' physiological maximum, it does represent the highest level of activity they are able to achieve. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline between group differences in age, length of illness and gender; Group 1 Number missing: 11, Reason: n=3 had dropped out of treatment (one had to return home to the United States, one injured his calf and decided not to continue, one could not be contacted at the time of follow-up); additional data missing due to patients refusing to have a second exercise test as they believed the initial test was harmful to them or failed to continue until they perceived themselves to have reached maximal effort, making their data invalid or their data could not be used due to equipment failure; Group 2 Number missing: 12, Reason: n=3 did not return follow-up questionnaires at 12 weeks; additional data missing due to patients refusing to have a second exercise test as they believed the initial test was harmful to them or failed to continue until they perceived themselves to have reached maximal effort, making their data invalid or their data could not be used due to equipment failure.	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study	Ng 2013[539]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=137)
Countries and setting	Conducted in Hong Kong (China); Setting: University teaching laboratory
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were included if they met the CDC 1994 criteria. They were screened on the phone. No mention of physical examination, etc.
Stratum	adults; severity mixed or unclear: Age 18-50, meeting CDC (Fukuda 1994) criteria for CFS - no further information on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Aged 18-50 years; met CDC diagnostic criteria for CFS
Exclusion criteria	History of alcohol/substance abuse; current medical conditions associated with fatigue
Recruitment/selection of patients	Participants recruited through press publicity in Hong Kong
Age, gender and ethnicity	Age - Mean (SD): acupuncture 39.6 (6.6) years; placebo 42.0 (6.5) years. Gender (M:F): 31/68. Ethnicity: Not reported
Further population details	-

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Extra comments	Baseline demographics reported for population that was analysed, n=99.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=68) Intervention 1: complementary therapies - acupuncture. Eight 30 minute sessions over 4 weeks. Each participant received the intervention in an individual room and lay on a bed. Acupuncture points were chosen in accordance with the theories of traditional Chinese medicine (TCM). Performed by experienced and registered TCM practitioner. 5 needles/plastic stands used for each session. Plastic stands used, as per the control group, however needles in experimental group were longer with sharp tips and penetrated the skin. Needle manipulation was performed at the beginning, middle, and end of the session. Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. type of intervention: Not stated/Unclear (n=69) Intervention 2: placebo or sham - placebo/sham. Eight 30 minute sessions over 4 weeks. Sham acupuncture was administered following the same treatment schedule as the experimental group. Each participant received the intervention in an individual room, lying on a bed. Performed by the same practitioner who delivered treatment to the experimental group. Before the trial the practitioner received special training in the administration of sham acupuncture. 5 needles inside needle stands were used. Specially designed needles were used - the needles were blunt and were held in place by a specially designed needle holder and plastic stand so that the needle provided only a pricking sensation on the skin without penetrating it. The same acupuncture points were used in the experimental and control groups. Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated/Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACUPUNCTURE versus SHAM ACUPUNCTURE Protocol outcome 1: Quality of life at longest follow up available	

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- Actual outcome for adults; severity mixed or unclear: SF-12 - physical subscale at 4 weeks; Group 1: mean 41.36 (SD 7.574); n=50, Group 2: mean 38.72 (SD 10.579); n=49; SF-12 0-100 (not explicitly stated) Top=High is good outcome; Comments: Baseline score (SD): acupuncture 34.43 (7.676); sham 34.99 (9.369); Effect size (Cohen's d): acupuncture 0.92; sham 0.38; net effect size 0.52
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation sounds like it could be alternation: Permuted-block randomization was employed to allocate participants, with the random sampling sequence following the manner of ECEC (E = experimental, and C = control); that is, assignment of participants to groups followed a chronological sequence.
; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, sex, education level, employment, previous acupuncture experience, baseline outcome scores; Blinding details: patient reported outcome; Group 1 Number missing: 18, Reason: n=6 did not accept random allocation; n=12 not reported; Group 2 Number missing: 20, Reason: n=4 did not accept random allocation; n=16 not reported

- Actual outcome for adults; severity mixed or unclear: SF-12 - mental subscale at 4 weeks; Group 1: mean 47.96 (SD 9.419); n=50, Group 2: mean 47.76 (SD 10.693); n=49; SF-12 0-100 (not explicitly stated) Top=High is good outcome; Comments: Baseline score (SD): acupuncture 38.89 (9.665); 40.52 (10.122); Effect size (Cohen's d): acupuncture 0.96; sham 0.70; net effect size 0.54
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Permuted blocked randomisation used - random sampling sequence following the manner of ECEC (E=experiment, C=control), that is, assignment to groups followed a chronological sequence.
Data collection was administered by a research assistant who knew the group allocations but was not involved in delivering the intervention - not clear if this person had direct contact with participants (which could influence how they filled out questionnaires); Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Age, gender, previous acupuncture experience, and baseline score comparable between groups; Blinding details: Sham acupuncture was designed to appear the same as real acupuncture, the differences being the needles were shorter, blunt and did not penetrate the skin.
; Group 1 Number missing: 18, Reason: Only patients completing 6 or more (out of 8) intervention sessions were included in analysis, reasons for non-completion not given and unclear if follow-up data was available for these participants; Group 2 Number missing: 20, Reason: Only patients completing 6 or more (out of 8) intervention sessions were included in analysis, reasons for non-completion not given and unclear if follow-up data was available for these participants

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue scale (14-item) - physical subscale at 4 weeks; Group 1: mean 22.29 (SD 6.439); n=50, Group 2: mean 23.7 (SD 6.528); n=49; Comments: Baseline score (SD): acupuncture 30.67 (5.257); sham 29.17 (5.397)
Chalder fatigue scale (14-item) scoring system would normally yield a maximum possible score of 24 in the physical subscale, however this does not fit with values reported in study (scoring used not reported); Effect size (Cohen's d): acupuncture 1.44; sham 0.92; net effect size 0.52

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation sounds like it could be alternation: Permuted-block randomization was employed to allocate participants, with the random sampling sequence following the manner of ECEC (E = experimental, and C = control); that is, assignment of participants to groups followed a chronological sequence; Range of scores unclear.
; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, sex, education level, employment, previous acupuncture experience, baseline outcome scores; Blinding details: patient reported outcome; Group 1 Number missing: 18, Reason: n=6 did not accept random allocation; n=12 not reported; Group 2 Number missing: 20, Reason: n=4 did not accept random allocation; n=16 not reported

- Actual outcome for adults; severity mixed or unclear: Chalder fatigue scale (14-item) - mental subscale at 4 weeks; Group 1: mean 13.65 (SD 5.122); n=50, Group 2: mean 14.82 (SD 4.558); n=49; Chalder fatigue scale (14-item) Unclear Top=High is poor outcome; Comments: Baseline score (SD): acupuncture 20.65 (5.122); sham 18.55 (5.042)
Chalder fatigue scale (14-item) scoring system would normally yield a maximum possible score of 18 in the mental subscale, however this does not fit with values reported in study (scoring used not reported); Effect size (Cohen's d): acupuncture 1.41; sham 0.78; net effect size 0.63
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation sounds like it could be alternation: Permuted-block randomization was employed to allocate participants, with the random sampling sequence following the manner of ECEC (E = experimental, and C = control); that is, assignment of participants to groups followed a chronological sequence; Range of scores unclear.
; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, sex, education level, employment, previous acupuncture experience, baseline outcome scores; Blinding details: patient reported outcome; Group 1 Number missing: 18, Reason: n=6 did not accept random allocation; n=12 not reported; Group 2 Number missing: 20, Reason: n=4 did not accept random allocation; n=16 not reported

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: GHQ-12 at 4 weeks; Group 1: mean 1.43 (SD 2.828); n=50, Group 2: mean 1.06 (SD 2.828); n=49; GHQ-12 0-12 Top=High is poor outcome; Comments: Baseline score (SD): acupuncture 4.98 (4.265); sham 4.88 (3.751)
Scores reported are most consistent with binary scoring system (range 0-12), but not reported in study; Effect size (Cohen's d): acupuncture 0.99; sham 1.16; net effect size 0.17
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation sounds like it could be alternation: Permuted-block randomization was employed to allocate participants, with the random sampling sequence following the manner of ECEC (E = experimental, and C = control); that is, assignment of participants to groups followed a chronological sequence.

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; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, sex, education level, employment, previous acupuncture experience, baseline outcome scores; Blinding details: patient reported outcome; Group 1 Number missing: 18, Reason: n=6 did not accept random allocation; n=12 not reported; Group 2 Number missing: 20, Reason: n=4 did not accept random allocation; n=16 not reported Protocol outcome 4: adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: Adverse events at 4 weeks; Group 1: 0/62, Group 2: 0/65; Comments: Participants included in safety analysis not reported - 62/65 participants accepted randomisation and participated in study Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Randomisation sounds like it could be alternation: Permuted-block randomization was employed to allocate participants, with the random sampling sequence following the manner of ECEC (E = experimental, and C = control); that is, assignment of participants to groups followed a chronological sequence. Number analysed for AEs not stated, assumed all that received treatment. ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, sex, education level, employment, previous acupuncture experience, baseline outcome scores; Blinding details: patient reported outcome; Group 1 Number missing: 6, Reason: did not accept random allocation; Group 2 Number missing: 6, Reason: did not accept random allocation	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; activity levels at longest follow up available; return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	FITNET trial: Nijhof 2012[541] (Nijhof 2011 [542])	Study
Study type	RCT (Patient randomised; Parallel)	Study type
Number of studies (number of participants)	1 (n=135)	Number of stud
Countries and setting	Conducted in Netherlands; Setting: Patients referred to outpatient clinic of department of paediatrics, UMCU.	Countries and s
Line of therapy	1st line	Line of therapy
Duration of study	Follow up (post intervention): 6 months	Duration of stu
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by a paediatrician specializing in CFS using CDC criteria	Method of asse condition
Stratum	young people; severity mixed or unclear (Age 12-18; severe fatigue and functional impairment defined as physical functioning on CHQ score <85 and/or school participation ≤85%, and fatigue severity subscale CIS-20 ≥40)	Stratum
Subgroup analysis within study	Not applicable	Subgroup analy
Inclusion criteria	Age 12-18; able to read and write Dutch; access to a computer with internet; met CDC criteria for CFS diagnosis; severe fatigue and functional impairment defined as physical functioning on CHQ score <85 and/or school participation ≤85%, and fatigue severity subscale CIS-20 ≥40	Inclusion criteri
Exclusion criteria	Primary depression, anxiety disorder, or suicidal risk, as assessed with computerised self-reported questionnaires and confirmed by assessment by a psychologist; cognitive retardation	Exclusion criter
Recruitment/selection of patients	consecutive	Recruitment/se
Age, gender and ethnicity	Age - Range of means: CBT/usual care: 15.9/15.8. Gender (M:F): 24/111. Ethnicity: Unclear	Age, gender an
		Further popula
		Extra comment

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Further population details		Indirectness of
Extra comments	CBT/usual care: high education level 41%/31%; duration of symptoms 16months/19 months; acute onset 16%/10%; gradual onset 56%/64%; onset after infection 28%/25%; school attendance <85% 94%/85%; fatigue severity (CIS) 51.2/51.6; Physical functioning (CHQ-CF87) 60.7/56.8; somatic complaints (CSI) 33.3/34.7; depression score(CDI) 11.6/11.0; anxiety score (STAIC) 32.7/32.2	Interventions
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.	
Interventions	(n=68) Intervention 1: Psychological and behavioural interventions - CBT. The FITNET program was run on a dedicated hospital network (in Dutch). The portal layout for the program was specifically designed for adolescents. Patients' data and e-mails were encrypted and securely stored on the UMCU mainframes to guarantee privacy and confidentiality. The FITNET program consisted of two sections. The psychoeducational section could be accessed after the adolescents received their log-in codes. The cognitive behavioural therapy section consisted of 21 interactive modules, accessible after activation by the therapist. The patients received support from trained cognitive behavioural psychotherapists from the ECCF, solely through e-consults. At the start of the trial, two therapists had several years of experience as behavioural therapists (5 years and 10 years), and three were in the first year of their practical training as behavioural therapists. All five were given equal caseloads of patients. The FITNET therapists were not involved in usual care. Patients were able to log in and compose and send e-mails at any time. According to an individually tailored treatment, therapists responded to the e-consults on a set day once a week and thereafter once every 2 weeks. The patient would receive an immediate response to an emergency email. Additionally, for emergency situations, telephone contact details were available to the patients. Parents followed a parallel program, and had the same frequency of e-mail contacts wherein results so far were discussed and new assignments were given. The parents' portal consisted of the module's content, psychoeducation, and an e-consult application. The patients' portal was more detailed than was the parents' with diaries, questionnaires, and a review function of all passed modules. Patients and parents had separate accounts with unique usernames and passwords, and were not able to see each other's e-consult responses, ensuring confidentiality in communication with the therapist. The parents of patients younger than 15 years were instructed to coach their children, whereas those of older patients were asked to encourage their children to take responsibility for their treatment. Return to full-time education was the aim of treatment and was discussed early in therapy. Patients assigned to	Funding RESULTS (NUM Protocol outcor - Actual outcom (SD 10.579); n= (9.369); Effect s

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	FITNET agreed not to undergo any further medical examinations or to receive other treatments for fatigue while undergoing treatment. The FITNET therapist and school mentor had at least one communication about school attendance and the school's effort to encourage treatment compliance. The school mentor acted as a coach, adviser, or tutor when needed. School mentors were sent a standard letter at the commencement of treatment asking them for their cooperation and consideration. Duration 6 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: FITNET is a comprehensive internet-based application based on existing protocols and a theoretical model of face-to-face CBT for adolescents, specifically for those with CFS and their parents, delivered by trained cognitive behavioural psychotherapists from the Expert Centre for Chronic Fatigue. The web portal was developed in cooperation with adolescents with CFS who critically appraised text, lay-out and structure. (n=67) Intervention 2: usual care - standard medical care. The patients in the control group were given usual care, which included individual or group-based rehabilitation programmes, cognitive behavioural therapy face-to-face, or graded exercise treatment, or both, by a physical therapist. Records were kept of all the care given. Duration 6 months. Concurrent medication/care: Adolescents assigned to usual care were given the opportunity to attend FITNET after 6 months. Indirectness: No indirectness Further details: 1. type of intervention: not applicable	Risk of bias: All Crossover - Low employed to all assignment of p ; Indirectness o acupuncture ex random allocati - Actual outcom (SD 10.693); n= (10.122); Effect Risk of bias: All - Low, Subgroup (E=experiment, Data collection this person had Comments: NA acupuncture wa ; Group 1 Numb completion not or more (out of these participan Protocol outcon - Actual outcom n=50, Group 2: Chalder fatigue with values rep Risk of bias: All Crossover - Low employed to all assignment of p
Funding	Academic or government funding (Netherlands Organization for health research and Development)	
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus STANDARD MEDICAL CARE Protocol outcome 1: General symptom scales longest follow up available - Actual outcome for young people; severity mixed or unclear: Self-rated improvement at 6 months; Group 1: 52/67, Group 2: 17/64; Comments: Answer "yes" to statement "I have completely recovered" or "I feel much better but still experience some symptoms". Other options were had the same complaints, or had become worse than with the previous measurement. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for most outcome variables, though different for duration of symptoms. Overall well-randomized groups; Group 1 Number missing: 1, Reason: 1 = recovered; Group 2 Number missing: 3, Reason: 1 = recovered, 2= not recovered but did not want to attend FU		

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Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Fatigue severity (CIS-20) at 6 months; Group 1: mean 24 (SD 13.4); n=67, Group 2: mean 42.3 (SD 13.1); n=64 Checklist individual strength-20 8-56 Top=High is poor outcome; Comments: Baseline scores (SD), CBT 51.2 (4.4), usual care 51.6 (4.6)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for most outcome variables, though different for duration of symptoms. Overall well-randomized groups; Group 1 Number missing: 1, Reason: 1 = recovered; Group 2 Number missing: 3, Reason: 1 = recovered, 2= not recovered but did not want to attend FU

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Physical functioning (CHQ-CF87) at 6 months; Group 1: mean 88.5 (SD 13.8); n=67, Group 2: mean 70.1 (SD 17.6); n=64 Child health questionnaire physical functioning sub scale 1-100% Top=High is good outcome; Comments: Baseline scores (SD), CBT 60.7 (14.5), usual care 56.8 (20.9)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for most outcome variables, though different for duration of symptoms. Overall well-randomized groups; Group 1 Number missing: 1, Reason: 1 = recovered; Group 2 Number missing: 3, Reason: 1 = recovered, 2= not recovered but did not want to attend FU

Protocol outcome 4: adverse events at longest follow up available
- Actual outcome for young people; severity mixed or unclear: serious adverse events at 6 months; Group 1: 0/67, Group 2: 0/64
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for most outcome variables, though different for duration of symptoms. Overall well-randomized groups; Group 1 Number missing: 1, Reason: 1 = recovered; Group 2 Number missing: 3, Reason: 1 = recovered, 2= not recovered but did not want to attend FU

Protocol outcome 5: return to school or work at longest follow up available
- Actual outcome for young people; severity mixed or unclear: mean school attendance at 6 months; Group 1: mean 84.3 % (SD 29.5); n=67, Group 2: mean 51.7 % (SD 34.1); n=64
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Similar for most outcome variables, though different for duration of symptoms. Overall well-randomized groups; Group 1 Number missing: 1, Reason: 1 = recovered; Group 2 Number missing: 3, Reason: 1 = recovered, 2= not recovered but did not want to attend FU

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Protocol outcor
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safety analysis

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Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; sleep quality at longest follow up available; activity levels at longest follow up available; Exercise performance measure at longest follow up available	Risk of bias: All Crossover - Low employed to all assignment of p Number analyse ; Indirectness o acupuncture ex random allocati
		Protocol outcor study

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Study	Núñez 2011[550]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Spain; Setting: Chronic Fatigue Unit, at a public, tertiary, university hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical history, physical exam, analytical tests (biochemical, hematological, hormonal, and immunological profile), chest X-ray, 12-lead electrocardiogram, and psychological evaluation, met CDC criteria
Stratum	Severity and age mixed or unclear: age not part of inclusion criteria but mean (SD) suggests adults; meeting CDC (Fukuda 1994) criteria; no further details on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Diagnosed with CFS according to Fukuda criteria
Exclusion criteria	Patients with any past or current diagnosis of a major depressive disorder with psychotic or melancholic features according to Fukuda criteria; patients with physical diseases that could cause fatigue; patients unable to participate fully in study procedures; patients involved in ongoing legal or occupational conflicts, such as disputes about work-loss due to CFS, that could have interfered with the evaluation
Recruitment/selection of patients	patients referred during the recruitment period to the CFS outpatient referral clinic by primary health care physicians due to prolonged, disabling fatigue of unknown origin of more than 6 months duration, meeting inclusion criteria

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Age, gender and ethnicity	Age - Mean (SD): intervention 42.65 (9.5), control 44.27 (10.76) years. Gender (M:F): 12/101. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=60) Intervention 1: Psychological and behavioural interventions - CBT. Cognitive behavioural therapy + graded exercise therapy in groups of 16 + conventional pharmacological symptomatic treatment. CBT (9 twice weekly 90 minute sessions) carried out by a clinical psychologist with 7 years' experience in CBT with the main objective to identify correct behavioural patterns and adaptive thought models and create a therapeutic link. Content included psychoeducational interventions to explain the multi-factorial character of CFS; progressive muscle relaxation procedures; sleep hygiene patterns; detection and control of verbal and non-verbal pain-inducing attitudes; cognitive restructuring to modify non-adapted and catastrophic thought patterns; information about the relationship between vegetative and anxiety symptoms; modification of type A behavioural patterns; improvement in assertiveness; patterns to increase attention and memory; sensorial focalization for sexual inhibition; and disease relapse prevention. GET included thrice-weekly 1-h sessions carried out in intermittent periods of 10 min for 3 months. Patients were informed that exercise was designed to restore their ability to do sustained physical exercise as far as possible. Gradual increases in aerobic exercise at a rate of 5 min per session and complementary activities such as flexibility exercise and relaxation therapy were introduced. Total exercise load was maintained or increased to a maximum of 40 min per day, according to individual tolerance. All GET sessions supervised by a qualified physiotherapist, who is a registered nurse with a diploma in physiotherapy, and more than 20 years' experience in general physiotherapy for neurological disease and 8 years' experience in a third-level CFS and fibromyalgia reference unit. CBT and GET administered in an integrated manner. Duration 3 months. Concurrent medication/care: Symptomatic pharmacological treatment included analgesia (paracetamol 1–3 g/day p.o.), ibuprofen (600–1800mg/day p.o.) if subjects reported inflammation (fever, myalgia, enlarged cervical nodes), and zolpidem 10 mg/ night p.o. if patients reported significant insomnia. No other treatment was admitted during the study period. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (physiotherapist had experience in CFS, unclear whether GET specifically designed for CFS, unclear whether CBT specifically designed for CFS or whether therapist had expertise/experience of CFS).

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	(n=60) Intervention 2: usual care - standard medical care. Usual CFS therapy including exercise counselling and conventional pharmacological symptomatic treatment. Exercise counselling performed by personal interview with the same physiotherapist and objective to provide activities that restored patient's ability to do sustained physical exercise as far as possible. Program included three daily 10-min sessions, performed in separate periods, with adapted aerobic exercise, including walking and home-stretching exercises. Symptomatic pharmacological treatment included analgesia (paracetamol 1–3 g/day p.o.), ibuprofen (600–1800mg/day p.o.) if subjects reported inflammation (fever, myalgia, enlarged cervical nodes), and zolpidem 10 mg/ night p.o. if patients reported significant insomnia. Duration study duration. Concurrent medication/care: No other treatment was admitted during the study period. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (Generalitat of Catalonia and CIBEROBN, Carlos III Health Institute, Majadahonda, Madrid)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MULTIDISCIPLINARY TREATMENT versus STANDARD MEDICAL CARE

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for Severity and age mixed or unclear: SF36 physical function at 12 months; Group 1: mean 32.63 (SD 22.52); n=58, Group 2: mean 38.28 (SD 22.73); n=57; SF36 physical function 0-100 Top=High is good outcome; Comments: Baseline values: intervention 39.69 (22.8), control 40.04 (22.09)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

- Actual outcome for Severity and age mixed or unclear: SF36 physical role at 12 months; Group 1: mean 4.39 (SD 15.76); n=58, Group 2: mean 9.82 (SD 26.41); n=57; SF36 physical role 0-100 Top=High is good outcome; Comments: Baseline values: intervention 8.33 (22.82), control 11.61 (28.19)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-

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attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance
- Actual outcome for Severity and age mixed or unclear: SF36 bodily pain at 12 months; Group 1: mean 21.81 (SD 21.43); n=58, Group 2: mean 29.34 (SD 21.58); n=57; SF36 bodily pain 0-100 Top=High is good outcome; Comments: Baseline values: intervention 27.09 (24.22), control 27.41 (19.04)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

- Actual outcome for Severity and age mixed or unclear: SF36 general health at 12 months; Group 1: mean 30.19 (SD 16.98); n=58, Group 2: mean 29.76 (SD 15.14); n=57; SF36 general health 0-100 Top=High is good outcome; Comments: Baseline values: intervention 29.96 (16.48), control 27.43 (14.9)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

- Actual outcome for Severity and age mixed or unclear: SF36 vitality at 12 months; Group 1: mean 15 (SD 15.06); n=58, Group 2: mean 18.66 (SD 16.11); n=57; SF36 vitality 0-100 Top=High is good outcome; Comments: Baseline values: intervention 16.14 (14.76), control 17.05 (15.37)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

- Actual outcome for Severity and age mixed or unclear: SF36 social function at 12 months; Group 1: mean 30.92 (SD 24.9); n=58, Group 2: mean 37.72 (SD 26.27); n=57; SF36 social function 0-100 Top=High is good outcome; Comments: Baseline values: intervention 34.21 (25.61), control 34.82 (24.85)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

- Actual outcome for Severity and age mixed or unclear: SF36 emotional role at 12 months; Group 1: mean 35.67 (SD 43.12); n=58, Group 2: mean 46.43 (SD 47.85); n=57; SF36 emotional role 0-100 Top=High is good outcome; Comments: Baseline values: intervention 28.07 (41.69), control 47.62 (48.77)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

- Actual outcome for Severity and age mixed or unclear: SF36 mental health at 12 months; Group 1: mean 46.25 (SD 21.57); n=58, Group 2: mean 50.86 (SD 20.58); n=57; SF36 mental health 0-100 Top=High is good outcome; Comments: Baseline values: intervention 44.7 (21.17), control 50.14 (22.54)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for Severity and age mixed or unclear: Stanford Health Assessment Questionnaire - global health status at 12 months; Group 1: mean 7.27 (SD 1.88); n=58, Group 2: mean 6.83 (SD 2.09); n=57; Patient global assessment visual analogue scale 0-10 Top=High is poor outcome; Comments: Baseline values: intervention 6.93 (2.23), control 7.21 (1.96)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Stanford Health Assessment Questionnaire at 12 months; Group 1: mean 1.27 (SD 0.72); n=58, Group 2: mean 1.14 (SD 0.66); n=57; Stanford Health Assessment Questionnaire 0-3 Top=High is poor outcome; Comments: Baseline values: 1.14 (0.73), control 1.05 (0.69)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance

Protocol outcome 4: Pain at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Stanford Health Assessment Questionnaire - pain intensity at 12 months; Group 1: mean 6.91 (SD 2.28); n=58, Group 2: mean 6.28 (SD 2.4); n=57; Pain intensity visual analogue scale 0-10 Top=High is poor outcome; Comments: Baseline values:

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intervention 6.51 (2.63), control 6.55 (2.33) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline epidemiological and clinical characteristics; SF-36 emotional role score was lower (worse) in the intervention group; Group 1 Number missing: 2, Reason: lost to follow up due to non-attendance; Group 2 Number missing: 3, Reason: lost to follow up due to non-attendance	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	O'Dowd, 2006 trial: O'Dowd 2006[553]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=153)
Countries and setting	Conducted in United Kingdom; Setting: Pain management centre in UK hospital.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: According to Fukuda criteria (CDC)
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Presentation consistent with CDC criteria; patient given informed consent
Exclusion criteria	Concurrent severe mental illness (i.e. psychosis and allied conditions); planned or concurrent rehabilitation; inability to attend all treatment sessions; ongoing physical investigations
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: CBT/EAS/SMC: 41.6/38.8/42.9. Gender (M:F): 51:102. Ethnicity: unclear
Further population details	-

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Extra comments	CBT/EAS/SMC: lives alone 14%/12%/22%; total number of symptoms 7/9/9; time since diagnosis >36 months 22%/34%/40%; psychological or psychiatric treatment for CFS previously 17%/13%/18%; current antidepressants 44%/46%/30%; required help because of CFS 68%/73%/66%;
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=52) Intervention 1: Psychological and behavioural interventions - CBT. The CBT used in this trial was designed to do two things: first to attempt to modify thoughts and beliefs about symptoms and illness, and second to attempt to modify behavioural responses to symptoms and illness, such as rest, sleep and activity. The ultimate goal of the treatment was to increase adaptive coping strategies and therefore reduce the distress and disability. The content of the programme included: ● Elucidation of core beliefs regarding their illness and its management. ● Monitoring of activity levels and introduction of appropriate timetable. ● Introduction to exercises designed to increase general level of fitness, balance and confidence in exercise. A range of aerobic, strength, balance and stretching exercises were taught. ● Behavioural modification of sleep patterns. ● Mood management advice. ● Goal setting. The CBT groups were introduced to a structured incremental exercise programme following a group discussion about the unhelpful nature of activity cycling, following CBT principles. The calculation of a deliberately low 'baseline' for exercise as a means of counteracting activity cycling was taught, and instructions were given about pacing up by small increments once the exercise level had been achieved successfully for several days (flexibility was allowed for patients to choose their own frequency of increments). Advice was given to patients to reduce the level of exercise considerably should a significant increase in symptoms be experienced at some stage in the future, and the balance between the risks and the benefits of prolonged rest during such a setback was explored. The management of setbacks was a specific subject included in the CBT group syllabus. Duration 14 weeks (8 fortnightly meetings, each lasting 2 hours). Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: CBT CFS-specific and delivered by 4 therapists with experience in chronic illness management (one with considerable experience with ME/CFS) (n=50) Intervention 2: Advice - occupational or school. Education and Support group (EAS). The same

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	therapists met with these groups, in the same setting, at the same time and for the same duration and frequency as the CBT groups. The focus of these groups was on the sharing of experiences and the learning of basic relaxation skills. Each week, a different relaxation exercise was taught. These groups served as a control for the non-specific effects of therapy and controlled for the effects of therapist time and attention. In order to validate the role of the physiotherapist within the EAS condition, a stretch programme was introduced. This included 16 stretches for major muscle groups in the body, and patients were advised to perform each stretch twice, in a relaxed manner. The purpose of the stretches was explained as loosening the muscles so that a state of relaxation in the muscles could be achieved. If further questions regarding exercise were asked in these groups, the group was informed that there was controversy regarding the value of aerobic exercise, and therefore we did not wish to introduce exercise if it were to be unhelpful for some patients. The physiotherapist also participated in the teaching of relaxation techniques, including in particular those that involved movement such as progressive muscle relaxation and slow diaphragmatic breathing. Duration 14 weeks. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: unclear whether relaxation intervention was CFS-specific; delivered by 4 therapists with experience in chronic illness management (one with considerable experience with ME/CFS) (n=51) Intervention 3: usual care - standard medical care. This group did not attend the hospital other than to complete the assessment material at baseline and 6 and 12 months. They continued to be managed in primary care. Duration 14 weeks. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus ADVICE - OCCUPATIONAL OR SCHOOL

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical at Pooled 6 and 12 months data; MD; -0.4 (95%CI -2.86 to 2.06, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number

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missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF36 mental at Pooled 6 and 12 months data; MD; 3.16 (95%CI -0.05 to 6.38, Units: 0-100, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Health status (HUI3) at Pooled 6 and 12 months data; MD; 0.023 (95%CI -0.0065 to 0.11, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue score at Pooled 6 and 12 months data; MD; -3.16 (95%CI -5.59 to -0.74, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: total words recalled at Pooled 6 and 12 months data; MD; 0.77 (95%CI -0.32 to 1.86, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 5, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: correct words at Pooled 6 and 12 months data; MD; 0.84 (95%CI -0.26 to 1.94, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 5, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: reaction time at Pooled 6 and 12 months data; MD; 0.99 (95%CI 0.9 to 1.08, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 5, Reason: unclear

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS anxiety at Pooled 6 and 12 months data; MD; -0.51 (95%CI -1.7 to 0.68, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: HADS depression at Pooled 6 and 12 months data; MD; -0.13 (95%CI -1.13 to 0.87, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

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- Actual outcome for adults; severity mixed or unclear: General health Questionnaire at Pooled 6 and 12 months data; MD; -1.8 (95%CI -4.17 to 0.57, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 5: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Normal walking speed at Pooled 6 and 12 months data; MD; 1.77 (95%CI 0.025 to 3.51, Units: shuttles, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Shuttles walked at Pooled 6 and 12 months data; MD; 1.16 (95%CI 0.94 to 1.43, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Perceived fatigue at Pooled 6 and 12 months data; MD; 1 (95%CI 0.86 to 1.16, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set). Baseline scores: CBT 3.0 (SD not reported; E&S 3.5 (SD not reported).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus STANDARD MEDICAL CARE

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical at Pooled 6 and 12 months data; MD; -1.63 (95%CI -4.05 to 0.78, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF36 mental at Pooled 6 and 12 months data; MD; 4.35 (95%CI 0.72 to 7.97, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Health status (HUI3) at Pooled 6 and 12 months data; MD; 0.029 (95%CI -0.052 to 0.11, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue score at Pooled 6 and 12 months data; MD; -2.61 (95%CI -4.92 to -0.3, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: total words recalled at Pooled 6 and 12 months data; MD; 0.69 (95%CI -0.47 to 1.86, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: correct words at Pooled 6 and 12 months data; MD; 0.80 (95%CI -0.3 to 1.89, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 15, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: reaction time at Pooled 6 and 12 months data; MD; 0.93 (95%CI 0.86 to 1.02, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS anxiety at Pooled 6 and 12 months data; MD; -1.27 (95%CI -2.52 to -0.02, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but

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small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: HADS depression at Pooled 6 and 12 months data; MD; -0.56 (95%CI -1.69 to 0.58, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: General health Questionnaire at Pooled 6 and 12 months data; MD; -2.21 (95%CI -4.52 to 0.1, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 5: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Normal walking speed at Pooled 6 and 12 months data; MD; 2.83 (95%CI 1.12 to 5.53, Units: shuttles, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Shuttles walked at Pooled 6 and 12 months data; MD; 1.2 (95%CI 0.99 to 1.45, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number

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missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Perceived fatigue at Pooled 6 and 12 months data; MD; 0.98 (95%CI 0.87 to 1.12, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set). Baseline scores: CBT 3.0 (SD not reported; UC 3.2 (SD not reported).
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 13, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADVICE - OCCUPATIONAL OR SCHOOL versus STANDARD MEDICAL CARE

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical at Pooled 6 and 12 months data; MD; -1.23 (95%CI -3.52 to 1.05, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF36 mental at Pooled 6 and 12 months data; MD; 1.19 (95%CI -2.26 to 4.63, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Health status (HUI3) at Pooled 6 and 12 months data; MD; 0.006 (95%CI -0.082 to 0.095, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue score at Pooled 6 and 12 months data; MD; 0.55 (95%CI -1.56 to 2.66, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: total words recalled at Pooled 6 and 12 months data; MD; -0.076 (95%CI -1.2 to 1.05, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: correct words at Pooled 6 and 12 months data; MD; -0.044 (95%CI -1.14 to 1.05, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 5, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: reaction time at Pooled 6 and 12 months data; MD; 0.95 (95%CI 0.87 to 1.03, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS anxiety at Pooled 6 and 12 months data; MD; -0.76 (95%CI -2 to 0.47, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: HADS depression at Pooled 6 and 12 months data; MD; -0.43 (95%CI -0.56 to 0.7, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: General health Questionnaire at Pooled 6 and 12 months data; MD; -0.41 (95%CI -2.8 to 1.98, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear

Protocol outcome 5: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Normal walking speed at Pooled 6 and 12 months data; MD; 1.06 (95%CI -0.37 to 2.49, Units: shuttles, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: Shuttles walked at Pooled 6 and 12 months data; MD; 1.04 (95%CI 0.86 to 1.24, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set.); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear - Actual outcome for adults; severity mixed or unclear: Perceived fatigue at Pooled 6 and 12 months data; MD; 0.99 (95%CI 0.87 to 1.13, Comments: ITT analysis. Pooled for 6 and 12 month treatments because no significant difference between time points. Adjusted for baseline scores and assessment set). Baseline scores: E&S 3.5 (SD not reported; UC 3.2 (SD not reported). Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some differences between groups in characteristics (such as gender) but small differences in outcome variables at baseline adjusted for in follow up analyses; Group 1 Number missing: 4, Reason: unclear; Group 2 Number missing: 7, Reason: unclear	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study	Oka 2014[558]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Japan; Setting: Outpatient
Line of therapy	Unclear
Duration of study	Intervention + follow up: 9.2 (SD 2.5) weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis of CFS was made for patients meeting the diagnostic criteria of the 1994 international research case definition (Fukuda), and did not include patients with idiopathic chronic fatigue
Stratum	adults; severity mixed or unclear: Adults age 20-70; level of fatigue serious enough to cause an absence from school or work for at least several days of a month but not serious enough to require assistance with activities of daily living
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients with CFS meeting the 1994 international research case definition (Fukuda criteria); aged 20-70 years old; fatigue did not improve sufficiently with ordinary treatment given for at least 6 months (e.g. antidepressants, Japanese traditional herbal medicine, coenzyme Q10, psychotherapy, GET, inpatient treatment program); level of fatigue serious enough to cause an absence from school or work for at least several days of a month but not serious enough to require assistance with the activities of daily living; able to fill out questionnaire without assistance; able to sit for at least 30 minutes; able to attend study appointments every 2-3 weeks

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Exclusion criteria	Fatigue due to a physical disease such as liver, kidney, heart, respiratory, endocrine, autoimmune, or malignant disease, severe anaemia, electrolyte abnormalities, obesity, or pregnancy; previously practiced yoga; idiopathic chronic fatigue.
Recruitment/selection of patients	Participants recruited from a CFS outpatient clinic
Age, gender and ethnicity	Age - Mean (SD): Yoga group 38.0 (11.1) years; control group 39.1 (14.2) years. Gender (M:F): 6/24. Ethnicity: Not reported
Further population details	-
Extra comments	NA
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=15) Intervention 1: complementary therapies - yoga. 20 minute sessions of isometric yoga, practiced on a one-to-one basis with an experienced yoga instructor, between 2-4pm on the day the patient's visited the hospital (every 2-3 weeks). Session performed in seated position without background music and consisted of breathing exercises and several repetitions of 6 poses performed at 50% of patient's maximal strength. The program was modified on a patient-to-patient basis depending on severity of fatigue and pain. Patients were also asked to practice this program at home on non-class days if they could with the digital and written aids. Patients were reviewed by a study doctor before and after each yoga session to check condition and for any changes/adverse events. Duration 9.2 (SD 2.5) weeks. Concurrent medication/care: Conventional pharmacotherapy - examples of pharmacotherapy used in the hospital department reported in the paper are antidepressants, Japanese traditional herbal medicine, coenzyme Q10, however it is not clear which pharmacotherapy treatments study participants received. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (Yoga instructor with over 30 years of experience; not clear if ME/CFS experience. Yoga programme was designed with consideration of CFS symptoms). (n=15) Intervention 2: usual care - standard medical care. Wait-list control group. Patient's visited the

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	hospital every 2-3 weeks. Duration 9.2 (SD 2.5) weeks. Concurrent medication/care: Conventional pharmacotherapy - examples of pharmacotherapy used in the hospital department reported in the paper are antidepressants, Japanese traditional herbal medicine, coenzyme Q10, however it is not clear which pharmacotherapy treatments study participants received. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (Japan Agency for Medical Research and Development)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: YOGA versus USUAL CARE/WAIT-LIST CONTROL Protocol outcome 1: Fatigue at longest follow up available - Actual outcome for young people; severity mixed or unclear: Chalder fatigue scale - total score at After the intervention period; Group 1: mean 19.2 (SD 7.5); n=15, Group 2: mean 25.8 (SD 5.9); n=15; Chalder fatigue scale 0-42 Top=High is poor outcome; Comments: Baseline score, mean (SD): yoga group 25.9 (6.1); control group 26.1 (6.2). Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Comparable for age, gender, baseline scores. Duration of illness not reported; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Ostojic 2016[563]
Study type	RCT (Patient randomised; Crossover: 2 months)
Number of studies (number of participants)	(n=21)
Countries and setting	Conducted in Serbia; Setting: Clinic
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 months (3 months initial intervention + 2 months washout + 3 months crossover)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Met 1994 CDC criteria for CFS. No further info on diagnosis.
Stratum	adults; severity mixed or unclear: Age >18 years; meeting 1994 CDC criteria for CFS; no info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Female; age >18 years; meeting 1994 CDC criteria for CFS
Exclusion criteria	Psychiatric comorbidity; use of any dietary supplement within 4 weeks prior to study commencing; unwillingness to return for follow-up; pregnant
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 39.3 (8.8) years. Gender (M:F): 0/21. Ethnicity: Not reported
Further population details	-
Extra comments	Weight 62.8 (8.5) kg, height 169.5 (5.8) cm.

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Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=21) Intervention 1: dietary supplementation – guanidinoacetic acid (GAA). 2.4g GAA per day, oral administration. Dose chosen as a dose that gives an increased plasma creatine concentration with minimum side effects in men and women. Duration 3 months. Concurrent medication/care: Participants were asked to maintain their usual lifestyle, dietary intake, and to not use any dietary supplements during the study. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable Comments: Half the patients were randomised to placebo and half to GAA for the first half of the study. After the washout period these groups switched, so all patients were allocated to placebo and intervention. (n=21) Intervention 2: placebo or sham - placebo. Placebo containing cellulose, oral administration. No further info. Duration 3 months. Concurrent medication/care: Participants were asked to maintain their usual lifestyle, dietary intake, and to not use any dietary supplements during the study. . Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable Comments: Half the patients were randomised to placebo and half to GAA for the first half of the study. After the washout period these groups switched, so all patients were allocated to placebo and intervention.
Funding	Academic or government funding (Serbian Ministry of Science; National Strength and Conditioning Association; Faculty of Sport and Physical Education)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANIDINOACETIC ACID (GAA) versus PLACEBO (CELLULOSE)

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 - physical common score at 3 months; Group 1: mean 55.2 (SD 2.8); n=14, Group 2: mean 52.8 (SD 4.2); n=14; SF-36 Not reported Top=High is good outcome; Comments: Baseline score (SD): 55.1 (4.9)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc which could influence subjective patient reported outcome; Group 1 Number missing: 7,

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Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

- Actual outcome for adults; severity mixed or unclear: SF36 - mental common score at 3 months; Group 1: mean 51.1 (SD 5.5); n=14, Group 2: mean 45.8 (SD 6.5); n=14; SF-36 Not reported Top=High is good outcome; Comments: Baseline score (SD): 42.4 (13.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - general fatigue at 3 months; Group 1: mean 11.6 (SD 1.3); n=14, Group 2: mean 11.8 (SD 1.5); n=14; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline score (SD): 12.1 (1.5)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - physical fatigue at 3 months; Group 1: mean 11.7 (SD 1.2); n=14, Group 2: mean 11.6 (SD 1.4); n=14; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline score (SD): 11.2 (1.0)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover

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study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - reduced activity at 3 months; Group 1: mean 11.7 (SD 1.8); n=14, Group 2: mean 13.9 (SD 1.2); n=14; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline score (SD): 11.7 (1.6)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at ‘baseline vs post-administration at 3 months’ – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - reduced motivation at 3 months; Group 1: mean 13.1 (SD 1.9); n=14, Group 2: mean 15 (SD 1.8); n=14; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline score (SD): 15.2 (1.5)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at ‘baseline vs post-administration at 3 months’ – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - mental fatigue at 3 months; Group 1: mean 12.2 (SD 1.7); n=14, Group 2: mean 14 (SD 0.9); n=14; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline score (SD): 12.9 (1.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

Protocol outcome 3: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: VAS - at rest at 3 months; Group 1: mean 1.2 (SD 1); n=14, Group 2: mean 1.4 (SD 1.3); n=14; Visual analogue scale (VAS) 0-10 Top=High is poor outcome; Comments: Baseline score (SD): 1.4 (1.1)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

- Actual outcome for adults; severity mixed or unclear: VAS - during activity at 3 months; Group 1: mean 4.4 (SD 1.5); n=14, Group 2: mean 5 (SD 1.8); n=14; Visual analogue scale 0-10 Top=High is poor outcome; Comments: Baseline score (SD): 5.0 (1.5)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Results reported at 'baseline vs post-administration at 3 months' – likely end of study results rather than first period results but not completely clear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome; Group 1 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost; Group 2 Number missing: 7, Reason: n=7 lost during the intervention period 'due to reasons not connected to the study per se'. No further info. Unclear at what stage of the study participants were lost.

Protocol outcome 4: Adverse events at longest follow up available

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- Actual outcome for adults; severity mixed or unclear: Side effects (self-reported) at 3 months; Group 1: 0/21, Group 2: 0/21; Comments: Number analysed not stated; presumed to be all participants. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Presumed all participants who received study treatment were included in safety analysis, but not reported. Open-ended questionnaire used - not described; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Crossover study so placebo and intervention groups are the same participants; Blinding details: Placebo or success of blinding not described in detail so unclear if participants could deduce allocation from appearance, taste, etc. which could influence subjective patient reported outcome. Side effects were self-reported by participants; Group 1 Number missing: Reason: Not reported; Group 2 Number missing: , Reason: Not reported.	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	**PACE trial: White 2011[847] (Bourke 2014[81], Dougall 2014[239], Sharpe 2015[676], Walwyn 2013[816], White 2007[848])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=641)
Countries and setting	Conducted in United Kingdom; Setting: Specialist CFS clinics in UK (2005-2008)
Line of therapy	1st line
Duration of study	Follow up (post intervention): 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Oxford Scale plus bimodal score of 6 or more on Chalder Fatigue scale and a score of 60 or less on SF36 physical (changed to <65 11 months post randomization to increase recruitment). Medically assessed by specialist clinic doctors to exclude alternative diagnoses.
Stratum	adults; severity mixed or unclear: All over 18, but severity not explicitly described
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	People with 'CFS/ME' attending 6 specialist CFS clinics; Oxford criteria positive [fatigue main symptom accompanied by significant disability, in the absence of an exclusionary medical or psychiatric diagnosis]; Score of 6 or more on Chalder fatigue scale; SF36 physical sub-scale score <60 (changed to <65 after 11 months post randomization to increase recruitment); no alternative diagnoses that would explain symptoms;
Exclusion criteria	<18 years; significant risk of self-harm; unable to attend hospital appointments; unable to read or speak English; medical needs that made participation inappropriate; previous participation in a PACE trial clinic (originally excluded anyone from any trial but dropped as nature of treatment given elsewhere hard to establish).
Recruitment/selection of patients	Consecutive

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Age, gender and ethnicity	Age - Mean (SD): 38 (12). Gender (M:F): 23:77. Ethnicity: 93% white
Further population details	-
Extra comments	International CFS criteria 62%; London ME criteria 56%; any depressive disorder 56%; any psychiatric disorder 47%; duration of illness (months) 32; BMI 25.5. Data from the follow up at a mean of 134 weeks was based on less data (SMC n=115, APT n=120, CBT n=119, GET n=127. After the 12 month treatment was over, 44% participants included in the later follow up started other non-protocol treatments such as CBT and GET. Most starting these (63%) were from the SMC and APT groups. An ITT approach has been correctly used, but this needs to be borne in mind when interpreting the 134 week data.
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=160) Intervention 1: Exercise interventions - GET. Standard medical care + graded exercise therapy (GET). GET was done on the basis of deconditioning and exercise intolerance theories of chronic fatigue syndrome. Therapeutic strategies consisted of establishment of a baseline of achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active. Target heart rate ranges were set when necessary to avoid overexertion, which eventually aimed at 30 min of light exercise five times a week. When this rate was achieved, the intensity and aerobic nature of the exercise was gradually increased, with participant feedback and mutual planning. The most commonly chosen exercise was walking. The therapy manual was based on that used in previous trials. GET was delivered by physiotherapists and one exercise physiologist. Duration 12 months. Concurrent medication/care: Treatments standardized by provision of manuals for doctors, therapists, and participants. At least three sessions of specialist medical care were offered to participants during the 12 months, and more were offered if clinically indicated. Up to 14 therapy sessions were offered during the first 23 weeks; the first four were once a week and subsequently they were once every 2 weeks. An additional booster session was offered at 36 weeks. No other additional sessions were offered. Most treatments were delivered face-to-face but some were provided by telephone. Treatment was provided individually although participants could be accompanied if they wanted. Indirectness: No indirectness Further details: 1. type of intervention: based on deconditioning and exercise intolerance theories of chronic fatigue syndrome; 4/11 therapists had previous experience in a CFS or chronic pain service

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	(n=161) Intervention 2: Psychological and behavioural interventions - CBT. Standard medical care + cognitive behavior therapy (CBT). CBT was done on the basis of the fear avoidance theory of chronic fatigue syndrome. Therapeutic strategies guided participants to address unhelpful cognitions, including fears about symptoms or activity by testing them in behavioural experiments. These experiments consisted of establishing a baseline of activity and rest and a regular sleep pattern, and then making collaboratively planned gradual increases in both physical and mental activity. Furthermore, participants were helped to address social and emotional obstacles to improvement through problem-solving. Therapy manuals were based on manuals used in previous trials. CBT was delivered mainly by clinical psychologists and nurse therapists. Duration 12 months. Concurrent medication/care: Treatments standardized by provision of manuals for doctors, therapists, and participants. At least three sessions of specialist medical care were offered to participants during the 12 months, and more were offered if clinically indicated. Up to 14 therapy sessions were offered during the first 23 weeks; the first four were once a week and subsequently they were once every 2 weeks. An additional booster session was offered at 36 weeks. No other additional sessions were offered. Most treatments were delivered face-to-face but some were provided by telephone. Treatment was provided individually although participants could be accompanied if they wanted. Indirectness: No indirectness Further details: 1. type of intervention: based on the fear avoidance theory of chronic fatigue syndrome; 7/13 therapists had previous experience in a CFS or chronic pain service (n=160) Intervention 3: self-management - adaptive pacing therapy. Standard medical care + adaptive pacing therapy (APT). APT was based on the envelope theory of chronic fatigue syndrome. Therapeutic strategies consisted of identifying links between activity and fatigue by use of a daily diary, with corresponding encouragement to plan activity to avoid exacerbations, developing awareness of early warnings of exacerbation, limiting demands and stress, regularly planning rest and relaxation, and alternating different types of activities, with advice not to undertake activities that demanded more than 70% of participants' perceived energy limits. Increased activities were encouraged, if the participant felt able, and as long as they did not exacerbate symptoms. Because this treatment had not been described in a manual, manuals were created for therapists and patients on the basis of previous descriptions, what pilot patients and clinicians reported as helpful, and with the advice of experienced therapists. Westcare and Action for ME helped in the design of the therapy and endorsed the final manuals. APT was provided by occupational therapists. Duration 12 months. Concurrent medication/care: Treatments standardized by provision of manuals for doctors, therapists, and participants. At least three sessions of specialist medical care were offered to

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	participants during the 12 months, and more were offered if clinically indicated. Up to 14 therapy sessions were offered during the first 23 weeks; the first four were once a week and subsequently they were once every 2 weeks. An additional booster session was offered at 36 weeks. No other additional sessions were offered. Most treatments were delivered face-to-face but some were provided by telephone. Treatment was provided individually although participants could be accompanied if they wanted. Indirectness: No indirectness Further details: 1. type of intervention: based on the envelope theory of chronic fatigue syndrome; 3/9 therapists had previous experience in a CFS or chronic pain service (n=160) Intervention 4: usual care - standard medical care. SMC was provided by doctors with specialist experience in chronic fatigue syndrome. All participants were given a leaflet explaining the illness and the nature of this treatment. The manual was consistent with good medical practice, as presently recommended. Treatment consisted of an explanation of chronic fatigue syndrome, generic advice, such as to avoid extremes of activity and rest, specific advice on self-help, according to the particular approach chosen by the participant (if receiving SMC alone), and symptomatic pharmacotherapy (especially for insomnia, pain, and mood). Duration 12 months. Concurrent medication/care: Treatments standardized by provision of manuals for doctors, therapists, and participants. At least three sessions of specialist medical care were offered to participants during the 12 months, and more were offered if clinically indicated. Up to 14 therapy sessions were offered during the first 23 weeks; the first four were once a week and subsequently they were once every 2 weeks. An additional booster session was offered at 36 weeks. No other additional sessions were offered. Most treatments were delivered face-to-face but some were provided by telephone. Treatment was provided individually although participants could be accompanied if they wanted. Indirectness: No indirectness Further details: 1. type of intervention: not applicable
Funding	Academic or government funding (UK MRC, DoH for England, UK department for work and pensions, and the Chief Scientist Office of the Scottish Government Health Directorates)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus ADAPTIVE PACING THERAPY (APT) Protocol outcome 1: Quality of life at longest follow up available - Actual outcome for adults; severity mixed or unclear: EQ-5D utilities at 52 weeks; Group 1: mean 0.59 (SD 0.3); n=143, Group 2: mean 0.54 (SD 0.29); n=148; EQ5D -0.594 - 1 Top=High is good outcome; Comments: Baseline values: GET 0.52 (0.26); APT 0.48 (0.27)	

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Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 17, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression scale - proportion with positive change (very much better or much better) at 134 weeks; OR; 1.4 (95%CI 0.8 to 2.3), Comments: GEE model comparing positive change to no/negative change.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 41, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 134 weeks; MD; -1.1 (95%CI -3 to 0.9), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 38, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 physical function subscale at 134 weeks; MD; 5.6 (95%CI -0.3 to 11.5), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: Failed to return questionnaire - their baseline

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data did not differ from those remaining; Group 2 Number missing: 40, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 5: Return to school/work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and Social Adjustment Scale at 134 weeks; MD; -2.1 (95%CI -4.5 to 0.3, Comments: linear mixed effect model);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 34, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 39, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining
Protocol outcome 6: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS depression scale at 52 weeks; MD; -0.5 (95%CI -1.23 to 0.23), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.18.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 10, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: HADS anxiety scale at 52 weeks; MD; -0.3 (95%CI -1.17 to 0.57), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.50.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 10, Reason: unclear

Protocol outcome 7: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain numeric rating scale at 52 weeks; Group 1: mean 1.69 (SD 1.38); n=144, Group 2: mean 2.07 (SD 1.42); n=151; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not

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reported and not adjusted for in analysis; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 8, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: joint pain numeric rating scale at 52 weeks; Group 1: mean 1.28 (SD 1.32); n=144, Group 2: mean 1.64 (SD 1.49); n=149; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 10, Reason: unclear

Protocol outcome 8: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 52 weeks; MD; -1.3 (95%CI -2.23 to -0.37), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0062.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 9: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: serious AEs at 52 weeks; Group 1: 13/160, Group 2: 15/159; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: non-serious AEs at 52 weeks; Group 1: 149/160, Group 2: 152/159; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as non-serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric

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disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 52 weeks; Group 1: 2/160, Group 2: 2/159. Comments: Serious adverse events were deemed 'adverse reactions' if independently judged to be a reaction to a trial intervention.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 10: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 min walk test at 52 weeks; MD; 41 (95%CI 20.53 to 61.47), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value <0.0001.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 50, Reason: unclear; Group 2 Number missing: 48, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus STANDARD MEDICAL CARE (SMC)

Protocol outcome 1: Quality of life at longest follow up
- Actual outcome for adults; severity mixed or unclear: EQ-5D utilities at 52 weeks; Group 1: mean 0.59 (SD 0.3); n=143, Group 2: mean 0.53 (0.31); n=151; EQ5D -0.594 - 1 Top=High is good outcome; Comments: Baseline values: GET 0.52 (0.26); SMC 0.50 (0.28)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 17, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression scale - proportion with positive change (very much better or much better) at 134 weeks; OR; 1.1 (95%CI 0.6 to 1.8); Comments: GEE model comparing positive change to no/negative change.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International

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CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 134 weeks; MD; -0.8 (95%CI -2.8 to 1.2), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 physical function subscale at 134 weeks; MD; 2 (95%CI -4 to 7.9, Comments: based on linear mixed effects model);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: did not return questionnaire; Group 2 Number missing: 45, Reason: did not return questionnaire

Protocol outcome 5: Return to school/work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and Social Adjustment Scale at 134 weeks; MD; -0.8 (95%CI -3.2 to 1.6, Comments: linear mixed effect model);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 33, Reason: questionnaires not returned; Group 2 Number missing: 45, Reason: questionnaires not returned

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Protocol outcome 6: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS depression scale at 52 weeks; MD; -1.1 (95%CI -1.84 to -0.36, Comments: Used adjusted model); 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0035.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 9, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: HADS anxiety scale at 52 weeks; MD; -1 (95%CI -1.8 to -0.2); Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.00142.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 7: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain numeric rating scale at 52 weeks; Group 1: mean 1.69 (SD 1.38); n=144, Group 2: mean 2.11 (SD 1.34); n=149; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 11, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: joint pain numeric rating scale at 52 weeks; Group 1: mean 1.28 (SD 1.32); n=144, Group 2: mean 1.54 (SD 1.48); n=151; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 8: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 52 weeks; MD; -1.4 (95%CI -2.3 to -0.5) ; Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0024.

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Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 9: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: serious AEs at 52 weeks; Group 1: 13/160, Group 2: 7/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: non-serious AEs at 52 weeks; Group 1: 149/160, Group 2: 149/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as non-serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 52 weeks; Group 1: 2/160, Group 2: 2/160. Comments: Serious adverse events were deemed ‘adverse reactions’ if independently judged to be a reaction to a trial intervention.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcome 10: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 min walk test at 52 weeks; MD; 35.3 (95%CI 16.84 to 53.76); Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0002.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 50, Reason: unclear; Group 2 Number missing: 42, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus ADAPTIVE PACING THERAPY

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: EQ-5D utilities at 52 weeks; Group 1: mean 0.63 (SD 0.28); n=143, Group 2: mean 0.54 (SD 0.29); n=148; EQ5D -0.594 - 1 Top=High is good outcome; Comments: Baseline values: CBT 0.54 (0.24); APT 0.48 (0.27)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression scale - proportion with positive change (very much better or much better) at 134 weeks; OR; 1.2 (95%CI 0.7 to 2);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 41, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 134 weeks; MD; -1.6 (95%CI -3.6 to 0.3), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42; Group 2 Number missing: 39

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Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 physical function subscale at 134 weeks; MD; 6.4 (95%CI 0.4 to 12.4), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 39, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 5: Return to school/work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and Social Adjustment Scale at 134 weeks; MD; -2.4 (95%CI -4.8 to 0.1);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 39, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 6: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS depression scale at 52 weeks; MD; -0.8 (95%CI -1.56 to -0.04), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0382.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 10, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: HADS anxiety scale at 52 weeks; MD; -0.7 (95%CI -1.45 to 0.05), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0671.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 10, Reason: unclear

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Protocol outcome 7: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain numeric rating scale at 52 weeks; Group 1: mean 1.73 (SD 1.33); n=145, Group 2: mean 2.07 (SD 1.42); n=151; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 8, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: joint pain numeric rating scale at 52 weeks; Group 1: mean 1.29 (SD 1.38); n=143, Group 2: mean 1.64 (SD 1.49); n=149; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 10, Reason: unclear

Protocol outcome 8: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 52 weeks; MD; -0.9 (95%CI -1.79 to -0.01) Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0466.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 9: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: serious AEs at 52 weeks; Group 1: 7/161, Group 2: 15/159; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0

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- Actual outcome for adults; severity mixed or unclear: non-serious AEs at 52 weeks; Group 1: 143/161, Group 2: 152/159; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as non-serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 52 weeks; Group 1: 3/161, Group 2: 2/159. Comments: Serious adverse events were deemed 'adverse reactions' if independently judged to be a reaction to a trial intervention.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 9: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 min walk test at 52 weeks; MD; 4.2 (95%CI -13.99 to 22.39), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.65.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 38, Reason: unclear; Group 2 Number missing: 48, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus STANDARD MEDICAL CARE (SMC)

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: EQ-5D utilities at 52 weeks; Group 1: mean 0.63 (SD 0.28); n=143, Group 2: mean 0.53 (SD 0.31); n=151; EQ5D -0.594 - 1 Top=High is good outcome; Comments: Baseline values: CBT 0.54 (0.24); SMC 0.50 (0.28).
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

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Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression scale - proportion with positive change (very much better or much better) at 134 weeks; OR; 0.9 (95%CI 0.5 to 1.5); Comments: GEE model comparing positive change to no/negative change.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 134 weeks; MD; -1.4 (95%CI -3.4 to 0.7); Comments: based on linear mixed effects model.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 physical function subscale at 134 weeks; MD; 2.8 (95%CI -3.2 to 8.8); Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 5: Return to school/work at longest follow up available

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- Actual outcome for adults; severity mixed or unclear: Work and Social Adjustment Scale at 134 weeks; MD; -1.1 (95%CI -3.6 to 1.4); Comments: linear mixed effect model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 42, Reason: questionnaires not returned; Group 2 Number missing: 45, Reason: questionnaires not returned

Protocol outcome 6: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS depression scale at 52 weeks; MD; -1.4 (95%CI -2.15 to -0.65); Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0003.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 9, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: HADS anxiety scale at 52 weeks; MD; -1.4 (95%CI -2.15 to -0.65); Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0003.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 7: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain numeric rating scale at 52 weeks; Group 1: mean 1.73 (SD 1.33); n=145, Group 2: mean 2.11 (SD 1.34); n=149; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 11, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: joint pain numeric rating scale at 52 weeks; Group 1: mean 1.29 (SD 1.38); n=143, Group 2: mean 1.54 (SD 1.48); n=151; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

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Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing:18, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 8: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 52 weeks; MD; -1.1 (95%CI -2.04 to -0.16); Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0216.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 9: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: serious AEs at 52 weeks; Group 1: 7/161, Group 2: 7/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: non-serious AEs at 52 weeks; Group 1: 143/161, Group 2: 149/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as non-serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 52 weeks; Group 1: 3/161, Group 2: 2/160. Comments: Serious adverse events were deemed ‘adverse reactions’ if independently judged to be a reaction to a trial intervention.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 10: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 min walk test at 52 weeks; MD; -1.5 (95%CI -19.52 to 16.52, Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.87.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 38, Reason: unclear; Group 2 Number missing: 42, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADAPTIVE PACING THERAPY (APT) versus STANDARD MEDICAL CARE (SMC)

Protocol outcome 1: Quality of life at longest follow up
- Actual outcome for adults; severity mixed or unclear: EQ-5D utilities at 52 weeks; Group 1: mean 0.54 (SD 0.29); n=148, Group 2: mean 0.53 (SD 0.31); n=151; EQ5D -0.594 - 1 Top=High is good outcome; Comments: Baseline values: APT 0.48 (0.27); SMC 0.50 (0.28)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 11, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression scale - proportion with positive change (very much better or much better) at 134 weeks; OR; 0.8 (95%CI 0.4 to 1.3); GEE model comparing positive change to no/negative change.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 41, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

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Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 134 weeks; MD; 0.3 (95%CI -1.7 to 2.3), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 39, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 physical function subscale at 134 weeks; MD; -3.6 (95%CI -9.6 to 2.4), Comments: based on linear mixed effects model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 41, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining; Group 2 Number missing: 45, Reason: Failed to return questionnaire - their baseline data did not differ from those remaining

Protocol outcome 5: Return to school/work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and Social Adjustment Scale at 134 weeks; MD; 1.3 (95%CI -1.2 to 3.7), Comments: linear mixed effect model;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 39, Reason: questionnaires not returned; Group 2 Number missing: 45, Reason: questionnaires not returned

Protocol outcome 6: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS depression scale at 52 weeks; MD; -0.6 (95%CI -1.34 to 0.14), Comments: Used adjusted

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model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.11.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 9, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: HADS anxiety scale at 52 weeks; MD; -0.7 (95%CI -1.46 to 0.06), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.0713.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 7: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain numeric rating scale at 52 weeks; Group 1: mean 2.07 (SD 1.42); n=151, Group 2: mean 2.11 (SD 1.34); n=149; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 8, Reason: unclear; Group 2 Number missing: 11, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: joint pain numeric rating scale at 52 weeks; Group 1: mean 1.64 (SD 1.49); n=149, Group 2: mean 1.54 (SD 1.48); n=151; numeric rating scale 0-4 Top=High is poor outcome; Comments: Baseline values not reported
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Baseline outcome values not reported and not adjusted for in analysis; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 8: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 52 weeks; MD; -0.1 (95%CI -0.75 to 0.55), Comments: Used adjusted model; 95% CI calculated from p-value, compared against forest plots reported in supplementary appendix – calculated confidence intervals appear slightly narrower. P-value 0.76.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria,

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meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 9, Reason: unclear; Group 2 Number missing: 9, Reason: unclear

Protocol outcome 9: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: serious AEs at 52 weeks; Group 1: 15/159, Group 2: 7/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: non-serious AEs at 52 weeks; Group 1: 152/159, Group 2: 149/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as non-serious adverse events, using an a priori guideline of seriousness.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 52 weeks; Group 1: 2/159, Group 2: 2/160. Comments: Serious adverse events were deemed ‘adverse reactions’ if independently judged to be a reaction to a trial intervention.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 10: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: 6 min walk test at 52 weeks; MD; -5.7 (95%CI -24.44 to 13.04), Comments: Used adjusted model; 95% CI calculated from p-value and visually confirmed against forest plots reported in supplementary appendix. P-value 0.55.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International

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CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Some baseline differences in outcomes, but these were adjusted for in the regression analyses; Group 1 Number missing: 48, Reason: unclear; Group 2 Number missing: 42, Reason: unclear

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus GET

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: EQ-5D utilities at 52 weeks; Group 1: mean 0.63 (SD 0.28); n=143, Group 2: mean 0.59 (SD 0.3); n=143; EQ5D -0.594 - 1 Top=High is good outcome; Comments: Baseline values: CBT 0.54 (0.24); GET 0.52 (0.26)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 17, Reason: unclear

Protocol outcome 2: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression scale - proportion with positive change (very much better or much better) at 134 weeks; Group 1: 50/119; Group 2: 61/127
Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 42, Reason: unclear; Group 2 Number missing: 33, Reason: unclear

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue questionnaire at 134 weeks; Group 1: mean 18.4 (SD 8.5); n=119, Group 2: mean 19.1 (SD 7.9); n=127; Chalder fatigue scale (11-item) 0-33 Top=High is poor outcome; Comments: Baseline values: CBT 27.7 (3.7); GET 28.2 (3.8)
Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 42, Reason: unclear; Group 2 Number missing: 33, Reason: unclear

Protocol outcome 4: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 Physical function subscale at 134 weeks; Group 1: mean 62.2 (27.2); n=119, Group 2: mean

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59.8 (27.6); n=127; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 39 (15.3); GET 36.7 (15.4)
Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 42, Reason: unclear; Group 2 Number missing: 33, Reason: unclear

Protocol outcome 5: Return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and social adjustment scale at 134 weeks; Group 1: mean 19.7 (10.2); n=119, Group 2: mean 19.4 (10.8); n=126; Work and social adjustment scale 0-40 (not explicitly stated in paper) Top=High is poor outcome; Comments: Baseline values: CBT 27.4 (6.2); GET 27.3 (6.3)
Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 42, Reason: unclear; Group 2 Number missing: 34, Reason: unclear

Protocol outcome 6: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS depression scale at 52 weeks; Group 1: mean 6.2 (3.7); n=143, Group 2: mean 6.1 (4.1); n=144; HADS depression 0-21 Top=High is poor outcome; Comments: Baseline values: CBT 8.3 (3.7); GET 8.2 (3.6)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 16, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: HADS anxiety scale at 52 weeks; Group 1: mean 6.8 (4.2); n=143, Group 2: mean 7.1 (4.5); n=144; HADS anxiety 0-21 Top=High is poor outcome; Comments: Baseline values: CBT 8.1 (4.3); GET 8.0 (4.2)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 16, Reason: unclear

Protocol outcome 7: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain numeric rating scale at 52 weeks; Group 1: mean 1.73 (1.33); n=145, Group 2: mean 1.69 (1.38); n=144; 5-point scale (0=not at all present, 4=present all of the time) 0-4 Top=High is poor outcome; Comments: Baseline values: not reported

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Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 16, Reason: unclear; Group 2 Number missing: 16, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: joint pain numeric rating scale at 52 weeks; Group 1: mean1.29 (1.38) ; n=143, Group 2: mean1.28 (1.32); n=144; 5-point scale (0=not at all present, 4=present all of the time) 0-4 Top=High is poor outcome; Comments: Baseline values: not reported

Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 16, Reason: unclear

Protocol outcome 8: Sleep quality at longest follow up available

- Actual outcome for adults; severity mixed or unclear: Jenkins sleep scale at 52 weeks; Group 1: mean 9.9 (5.3); n=143, Group 2: mean 9 (4.8); n=144; Jenkins sleep scale 0-20 (not explicitly stated in paper) Top=High is poor outcome; Comments: Baseline values: CBT 12.5 (4.9); GET 11.7 (4.3)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 16, Reason: unclear

Protocol outcome 9: Adverse events at longest follow up available

- Actual outcome for adults; severity mixed or unclear: serious AEs at 52 weeks; Group 1: 7/161, Group 2: 13/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as serious adverse events, using an a priori guideline of seriousness.

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: non-serious AEs at 52 weeks; Group 1: 143/161, Group 2: 149/160; Comments: Adverse events were any new health related event reported by the participant in any context (treatment related or not). These were independently judged as non-serious adverse events, using an a priori guideline of seriousness.

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; adverse events included treatment-related and non-treatment related. Baseline details: All groups

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very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: serious adverse reactions at 52 weeks; Group 1: 3/161, Group 2: 2/160; Comments: Serious adverse events were deemed 'adverse reactions' if independently judged to be a reaction to a trial intervention. Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 10: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: 6 min walk test at 52 weeks; Group 1: mean 354 (106) n=123, Group 2: mean 379 (100); n=110; Distance (m); Comments: Baseline values: CBT 333 (86); GET 312 (87) Risk of bias: All domain – Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: All groups very similar in terms of age, sex, ethnicity, meeting International CFS criteria, meeting London ME criteria, any depressive disorder, any psychiatric disorder, duration of ME and BMI. Similar baseline outcome value. Group 1 Number missing: 38, Reason: unclear; Group 2 Number missing: 50, Reason: unclear	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Activity levels at longest follow up available

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Study	Pinxsterhuis 2017[591]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=146)
Countries and setting	Conducted in Norway; Setting: Community setting, six municipalities
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by a physician or medical specialist; meeting CDC criteria and Canadian diagnostic criteria
Stratum	adults; severity mixed or unclear: Age >18 years; required that patients be physically able to attend the program - no further info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Adults age >18 years; diagnosed by a physician or medical specialist; meeting CDC criteria and Canadian diagnostic criteria; able to read and speak Norwegian; physically able to attend the program
Exclusion criteria	Pregnant
Recruitment/selection of patients	Patients were recruited from four southern Norwegian towns and two suburbs in Oslo; various sources - waitlists for education program at hospital, patient organisations for CFS, healthcare professionals
Age, gender and ethnicity	Age - Mean (SD): intervention group 44.0 (11.8) years; control group 43.8 (11.6) years. Gender (M:F): 16/121. Ethnicity: Not reported
Further population details	-

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Extra comments	Years since diagnosis, median: intervention group 3 years (range 1-21, IQR 3); control group 3 (range 0-17, IQR 3) Baseline characteristics are reported for randomized population who continued to participate in study after randomisation (n=137)
Indirectness of population	No indirectness: NA
Interventions	(n=73) Intervention 1: self-management - self-management programmes. A self-management program consisting of eight group sessions (6-14 participants per group) every second week, 2.5 hour duration. Conducted by a peer counsellor (an experienced individual with CFS) and occupational therapist who had participated in a three-day training program. They followed a detailed manual to teach the self-management program. Program based on self-efficacy theory and energy limits theory (pacing). Participants were taught how to take greater initiative for coping with their illness and for dealings with healthcare professionals and significant others through educational presentations, the exchange of experiences among participants, modelling of self-management skills, guided mastery practice, and informative feedback. Topics covered included activity pacing, physical exercise, nutrition, economic self-sufficiency, personal relationships, available treatments, relaxation exercises. All educational presentations were given by healthcare professionals at the 'CFS/ME' centre. Participants also set personal goals/action plans, which were evaluated and adjusted if necessary, at each session. One educational session was also organised for relatives of participants. Duration 15 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (Intervention delivered by peer counsellor (experienced individual with CFS) and an occupational therapist after they participated in a 3 day training program. Educational presentations given by healthcare professionals at ME/CFS centre). (n=73) Intervention 2: usual care - standard medical care. Participants were allowed to receive treatment as usual, which is not standardised for CFS in Norway, but they were excluded from participation in the regular patients education program at the study hospital. Duration 15 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable

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Funding	Academic or government funding (Norwegian Foundation for Health and Rehabilitation; National Advisory Unit for ME/CFS)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GROUP-BASED SELF-MANAGEMENT PROGRAM versus USUAL MEDICAL CARE

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 mental component summary at 1 year; Group 1: mean 39.1 (SD 10.6); n=58, Group 2: mean 40.5 (SD 8.8); n=59; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores, mean (SD): intervention group 37.7 (9.9); control group 39.3 (10.9). MCS scores calculated using oblique scores, based on Norwegian reference data.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Imputation used when less than 50% of values on subscale were missing - only 0.002% of values were imputed; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, time since diagnosis, baseline scores, and a number of other factors. More females in intervention group but still the majority in both groups (94% vs 81%); Blinding details: Subjective patient assessed outcome; Group 1 Number missing: 14, Reason: n=2 did not accept participation due to ill-health; lost to follow-up – n=1 due to ill-health, n=1 moved to another town, n=10 refused the evaluations; Group 2 Number missing: 14, Reason: Did not accept participation - n=1 due to ill-health, n=1 not accepting randomisation; n=5 unknown reasons; lost to follow-up - n=1 due to ill-health, n=6 refused the evaluations

- Actual outcome for adults; severity mixed or unclear: SF-36 physical component summary at 1 year; Group 1: mean 24.7 (SD 8); n=58, Group 2: mean 24.2 (SD 8.5); n=59; SF-36 0-100 Top=High is good outcome; Comments: Baseline scores, mean (SD): intervention group 24.9 (7.0); control group 24.0 (7.0) PCS scores calculated using oblique scores, based on Norwegian reference data.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Imputation used when less than 50% of values on subscale were missing - only 0.002% of values were imputed; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, time since diagnosis, baseline scores, and a number of other factors. More females in intervention group but still the majority in both groups (94% vs 81%); Blinding details: Subjective patient assessed outcome; Group 1 Number missing: 14, Reason: n=2 did not accept participation due to ill-health; lost to follow-up – n=1 due to ill-health, n=1 moved to another town, n=10 refused the evaluations; Group 2 Number missing: 14, Reason: Did not accept participation - n=1 due to ill-health, n=1 not accepting randomisation; n=5 unknown reasons; lost to follow-up - n=1 due to ill-health, n=6 refused the evaluations

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue severity scale at 1 year; Group 1: mean 56.4 (SD 6.9); n=59, Group 2: mean 57.1 (SD 6.7); n=59; Fatigue severity scale 9-63 Top=High is poor outcome; Comments: Baseline scores, mean (SD): intervention group 56.0 (5.9); control group 58.3 (3.9)

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Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Imputation used when less than 50% of values on subscale were missing - only 0.002% of values were imputed; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, time since diagnosis, baseline scores, and a number of other factors. More females in intervention group but still the majority in both groups (94% vs 81%); Blinding details: Subjective patient assessed outcome; Group 1 Number missing: 14, Reason: n=2 did not accept participation due to ill-health; lost to follow-up – n=1 due to ill-health, n=1 moved to another town, n=10 refused the evaluations; Group 2 Number missing: 14, Reason: Did not accept participation - n=1 due to ill-health, n=1 not accepting randomisation; n=5 unknown reasons; lost to follow-up - n=1 due to ill-health, n=6 refused the evaluations	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study (subsidiary papers)	Powell 2001[601]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=148)
Countries and setting	Conducted in United Kingdom; Setting: secondary care
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients were assessed by a consultant physician to confirm the diagnosis
Stratum	Age and severity mixed or unclear (mean age and SD suggest majority were adults)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 15-55 who fulfilled the Oxford criteria for chronic fatigue syndrome and scored <25 on the physical functioning subscale of the SF-36 questionnaire (range 10 to 30, where 10 indicates maximum physical limitation in self-care and 30 indicates ability to do vigorous sports.
Exclusion criteria	having further physical investigations or taking other treatments including antidepressants (unless the same dose had been taken for at least three months without improvement); had a psychotic illness, somatisation disorder, eating disorder, or history of substance misuse; or were confined to a wheelchair or bed
Recruitment/selection of patients	Consecutive patients referred to chronic fatigue clinic at The Royal initially recruited from consecutive referrals to a dedicated chronic fatigue clinic at the Royal Liverpool University Hospital; because the clinic closed, recruitment continued from an infectious diseases outpatient clinic at University Hospital Aintree.

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Age, gender and ethnicity	Age - Mean (SD): intervention group: 32.98 (10.34); control group: 36.82 (10.51). Gender (M:F): 32/116. Ethnicity: not specified
Further population details	-
Extra comments	There is a number of patients reported not to have a definitive diagnosis by by a GP on admission to the trial (n=13/34 for the control group; n=42/114). Patients were randomised into four groups (three intervention groups and one control group); the graded exercise program for the intervention groups was the same, the only difference being in whether or not patients also received telephone contacts or face to face treatment sessions; thus data across the three intervention groups have been combined and reported as one intervention group vs control group
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=114) Intervention 1: Exercise interventions - GET. All patients had received a medical assessment followed by evidence-based explanations of symptoms that encouraged graded activity. Explanation of symptoms focused on circadian dysrhythmia, physical deconditioning and sleep abnormalities. A graded exercise program was designed in collaboration with each patient and tailored to his or her functional abilities. Once patients were successfully engaged in treatment, the role of predisposing and perpetuating psychosocial factors was discussed. Treatment was supported by an educational information pack that reiterated the verbal explanations. Patients were advised they would be sent questionnaires for assessment at three, six, and 12 months. Patients received two face to face sessions totalling three hours in which symptoms were explained and the graded exercise programme was designed (minimum intervention group, n=37); In addition to the minimum intervention patients (n=39) received seven planned telephone contacts, each about 30 minutes over three months, during which explanations for symptoms and the treatment rationale were reiterated and problems associated with graded exercise were discussed with the use of motivational interviewing techniques (telephone intervention) or in addition to the minimum intervention, patients (n=38) received seven one hour face to face treatment sessions over three months (maximum intervention), which had the same function as the telephone sessions in the telephone intervention group. . Duration 12 months. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: not stated/unclear Comments: Patients were randomised into four groups (three intervention groups and one control group);

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	the graded exercise program for the intervention groups was the same and the intervention groups differed in the method and number of treatment sessions, particularly in whether or not patients also received telephone contacts or face to face treatment sessions; thus data across the three intervention groups have been combined and reported as one intervention group vs control group (n=34) Intervention 2: usual care - standard medical care. patients received standardised medical care. This comprised a medical assessment, advice and an information booklet that encouraged graded activity and positive thinking but gave no explanations to for the symptoms. Patients were advised they would be sent questionnaires to assess their progress at three, six and 12 months and discharged back to primary care. Duration 12 months. Concurrent medication/care: not specified. Indirectness: Serious indirectness; Indirectness comment: included element of the intervention in that graded activity was encouraged Further details: 1. type of intervention: not stated/unclear
Funding	Other (Lindbury Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus CONTROL

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Fatigue at 12 months; Chalder fatigue scale: Group 1: mean 3.27 (SD 4.21); n=114, Group 2: mean 10.1 (SD 2.08); n=34; Comments: scores > 3 indicate excessive fatigue; GET group scores combined from three intervention groups; All SDs calculated since 95% CIs were reported

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Randomisation was stratified for scores on the hospital anxiety and depression scale, using cut off of 11 to indicate clinical depression; Group 1 Number missing: 19, Reason: dropped out due to: medical reasons (n=8); psychiatric reasons (n=7); no reason given (n=4), emigration (n=1), dissatisfaction with treatment (n=1); Group 2 Number missing: 2, Reason: dropped out; reason not stated

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Physical functioning at 12 months; SF-36 physical functioning: Group 1: mean 24.74 (SD 5.09); n=114, Group 2: mean 16.9 (SD 4.46); n=34; Comments: 10 indicates maximum physical limitation in self-care; 30 indicates ability to do vigorous sports; GET group scores combined from three intervention groups; All SDs calculated since 95% CIs were reported

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Randomisation was stratified for scores on the hospital anxiety and depression scale,

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using cut off of 11 to indicate clinical depression; Group 1 Number missing: 19, Reason: dropped out due to: medical reasons (n=8); psychiatric reasons (n=7); no reason given (n=4), emigration (n=1), dissatisfaction with treatment (n=1); Group 2 Number missing: 2, Reason: dropped out; reason not stated Protocol outcome 3: Psychological status at longest follow up available - Actual outcome for Severity and age mixed or unclear: HADS Depression at 12 months; Group 1: mean 4.36 (SD 4); n=114, Group 2: mean 10.1 (SD 4.76); n=34 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Randomisation was stratified for scores on the hospital anxiety and depression scale, using cut off of 11 to indicate clinical depression; Group 1 Number missing: 19, Reason: dropped out due to: medical reasons (n=8); psychiatric reasons (n=7); no reason given (n=4), emigration (n=1), dissatisfaction with treatment (n=1); Group 2 Number missing: 2, Reason: dropped out; reason not stated - Actual outcome for Severity and age mixed or unclear: HADS Anxiety at 12 months; Group 1: mean 7.11 (SD 4.41); n=114, Group 2: mean 10.1 (SD 4.76); n=34; HAD 0-21, score >10 indicates anxiety Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Randomisation was stratified for scores on the hospital anxiety and depression scale, using cut off of 11 to indicate clinical depression; Group 1 Number missing: 19, Reason: dropped out due to: medical reasons (n=8); psychiatric reasons (n=7); no reason given (n=4), emigration (n=1), dissatisfaction with treatment (n=1); Group 2 Number missing: 2, Reason: dropped out; reason not stated Protocol outcome 4: Sleep quality at longest follow up available - Actual outcome for Severity and age mixed or unclear: Jenkins Sleep problems questionnaire at 12 months; Group 1: mean 7.48 (SD 5.21); n=114, Group 2: mean 11.5 (SD 5.65); n=34 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Randomisation was stratified for scores on the hospital anxiety and depression scale, using cut off of 11 to indicate clinical depression; Group 1 Number missing: 19, Reason: dropped out due to: medical reasons (n=8); psychiatric reasons (n=7); no reason given (n=4), emigration (n=1), dissatisfaction with treatment (n=1); Group 2 Number missing: 2, Reason: dropped out; reason not stated	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Ridsdale 2001[631]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in United Kingdom; Setting: 10 general practices.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were assessed at baseline for ME/CFS using CDC 1994 criteria. Prior to study entry all participants were required to have had blood tests performed by a doctor, and a doctors assessment of physical health problems to ensure they were not the cause of fatigue.
Stratum	Severity and age mixed or unclear: Inclusion criteria age 16-75, though mean age (SD) which suggest the majority of participants were adults.
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Aged 16-75 years old; complains of fatigue as a main or important problem; 3 months' duration or more of fatigue symptoms; doctor performed a CBC, ESR, and thyroid function tests on entry or in the previous 6 months, and the results were normal; may have concurrent physical problems but, in the doctor's judgement, they have not caused the fatigue symptoms; no recent change in drug regimen.
Exclusion criteria	Score of <4 on fatigue questionnaire (bi-modal scoring); psychotic illness; patient unable to read English; learning difficulty precludes completion of questionnaires; current treatment from a psychiatrist, psychologist, community psychiatric nurse, or

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	counsellor; patient unable to attend the doctors' premises for therapy sessions.
Recruitment/selection of patients	Doctors were asked to recruit all patients who were suitable for the study.
Age, gender and ethnicity	Age - Mean (SD): counselling 37.7 (13.0) years; CBT 41.2 (13.9). Gender (M:F): 43:117. Ethnicity: Unclear
Further population details	-
Extra comments	Mean (SD): duration of fatigue (months) - 38.2 (40.8), history of anxiety or depression - 58%. Baseline population characteristics and inclusion criteria are for entire study population which includes patients without ME/CFS. Results for participants meeting CDC 1994 criteria for ME/CFS are reported separately - all patients were assessed at baseline to see if they conformed to these criteria, however the analysis of results in this subgroup is reported to be post-hoc.
Indirectness of population	Serious indirectness: CDC 1994 criteria used; PEM is not a compulsory feature.
Interventions	(n=20) Intervention 1: Psychological and behavioural interventions - CBT. Six sessions of up to one hour led by qualified CBT therapists with experience in primary care and supervised by the study authors. All therapists used the first session for assessment and engagement. CBT included providing a treatment rationale, activity planning, homework, establishing a sleep routine and other cognitive interventions. It was based on a model of understanding fatigue that makes a distinction between precipitating and perpetuating factors. Perpetuating factors were the focus of the intervention. The four main areas focused on were: the fatigue was managed by insuring that levels of activity and rest were both consistent and realistic given the patient's responsibilities; sleep disturbance was addressed using conventional methods; negative beliefs regarding the symptom of fatigue, self-expectations or self-esteem were identified and patients were encouraged to challenge them in the conventional way; specific lifestyle changes

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	were encouraged if deemed appropriate. A clear rationale for treatment was provided after a thorough assessment and relapse prevention was addressed in the last two sessions. Duration 3 months. Concurrent medication/care: those receiving treatment from a psychiatrist, psychologist, community psychiatric nurse, or counsellor were excluded. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (intervention specific to CFS but unclear whether therapsists were specialised in CFS). (n=25) Intervention 2: Psychological and behavioural interventions - counselling. Six sessions of up to one hour led by qualified counsellors with experience in primary care and supervised by the study authors. All therapists used the first session for assessment and engagement. The manual that was used in this trial was originally devised for a trial of counselling for patients with depression and mixed anxiety and depression in primary care. This model of counselling is non-directive and client-centred; it offers the patient an opportunity to talk through their concerns and difficulties in a non-judgmental and supportive environment. The aim of such counselling is to help patients to understand themselves better, to suggest alternative understandings, to uncover the links between current distress and past experience, and to provide the conditions for growth and healing. Duration 3 months. Concurrent medication/care: those receiving treatment from a psychiatrist, psychologist, community psychiatric nurse, or counsellor were excluded. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: other interventions (manual was originally devised for a trial of counselling for patients with depression and mixed anxiety and depression).
Funding	Other (Wellcome Trust (politically and financially independent foundation))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus COUNSELLING

Protocol outcome 1: Fatigue at longest follow up available

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- Actual outcome for Severity and age mixed or unclear: Chalder fatigue scale at 6 months ; Group 1: mean 20.8 (SD 9.7); n=17, Group 2: mean 18.6 (SD 8.4); n=20; Chalder fatigue scale 0-33 Top=High is poor outcome; Comments: Baseline values not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details reported for entire study sample, not separately for those meeting the CDC criteria ; Group 1 Number missing: 3, Reason: unclear; reasons reported for entire study population; Group 2 Number missing: 5, Reason: unclear; reasons reported for entire study population Protocol outcome 2: Psychological status at longest follow up available - Actual outcome for Severity and age mixed or unclear: Hospital anxiety and depression scale - Anxiety at 6 months ; Group 1: mean 11.4 (SD 3.8); n=17, Group 2: mean 9.6 (SD 5); n=20; HADS anxiety 0-21 Top=High is poor outcome; Comments: Baseline values not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details reported for entire study sample, not separately for those meeting the CDC criteria ; Group 1 Number missing: 3, Reason: unclear; reasons reported for entire study population; Group 2 Number missing: 5, Reason: unclear; reasons reported for entire study population - Actual outcome for Severity and age mixed or unclear: Hospital anxiety and depression scale - Depression at 6 months ; Group 1: mean 10.1 (SD 4.2); n=17, Group 2: mean 7.6 (SD 4.2); n=20; HADS depression 0-21 Top=High is poor outcome; Comments: Baseline values not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline details reported for entire study sample, not separately for those meeting the CDC criteria ; Group 1 Number missing: 3, Reason: unclear; reasons reported for entire study population; Group 2 Number missing: 5, Reason: unclear; reasons reported for entire study population	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; General symptom scales at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Ridsdale 2004[630]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=123)
Countries and setting	Conducted in United Kingdom; Setting: 22 general practices in London and South East England
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chronic fatigue syndrome (CFS) status was determined, using the CDC criteria (Fukuda et al. 1994)
Stratum	Severity and age mixed or unclear: age 16-75 years but mean (SD) suggests adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	for entire study sample: aged 16 to 75 years; complains of fatigue as a main or important problem; duration of fatigue symptoms for ≥3 months; no recent change in drug regimen; normal full blood count, erythrocyte sedimentation rate and thyroid function test on entry or in the previous 6 months
Exclusion criteria	for entire study sample: patient unable to read English; concurrent physical problems, which in the judgement of the doctor have caused the fatigue symptoms; patient has asthma and/or ischaemic heart disease that would contraindicate a physical step-test; psychotic illness, organic brain syndrome, or substance dependency; current treatment from a psychiatrist, psychologist, community psychiatric nurse, physiotherapist, or exercise therapist.

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Recruitment/selection of patients	from GP practices
Age, gender and ethnicity	Age - Mean (SD): for entire study sample: CBT 40 (12.3), GET 40 (10.8) years. Gender (M:F): entire study sample: 39/84. Ethnicity: not reported
Further population details	-
Extra comments	36 participants met CDC criteria at baseline.
Indirectness of population	Serious indirectness: CDC criteria; PEM not a compulsory feature
Interventions	(n=15) Intervention 1: Psychological and behavioural interventions - CBT. 6 x 45-min sessions over 12 weeks, with the first session used to assess and engage with the patient by cognitive behavioural therapists. After an assessment, a rationale for treatment is provided. The treatment involves activity planning, homework, establishing a sleep routine and other cognitive interventions (Chalder et al. 1999). It is based on a model that distinguishes between precipitating and perpetuating factors, with the perpetuating factors becoming the focus of the intervention. The treatment ensures levels of activity and rest are both consistent and realistic given the patients' responsibilities. Sleep disturbance and negative beliefs regarding the symptom of fatigue, self-expectations or self-esteem are identified and patients are encouraged to challenge them in the conventional way. Specific lifestyle changes are encouraged if deemed appropriate and relapse prevention is addressed in the last two sessions. Duration 12 weeks. Concurrent medication/care: those receiving current treatment from a psychiatrist, psychologist, community psychiatric nurse, physiotherapist, or exercise therapist were excluded. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (CBT specific for CFS but unclear whether therapists are specialised in CFS). (n=21) Intervention 2: Exercise interventions - GET. 6 x 45-min sessions over 12 weeks, with the first session used to assess and engage with the patient by

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	physiotherapists. Based on the principles of exercise prescription devised by the American College of Sports Medicine (American College of Sports Medicine, 2000), adapted to each patient's current physical capacity. It was developed from a GET protocol designed for patients with chronic fatigue syndrome in a specialist context (Fulcher & White, 1998). GET is structured and supervised activity management that aims for a gradual but progressive increase in aerobic activities, usually walking. Home exercise is programmed, with initial sessions lasting between 5 and 15 min at an intensity of 50% of the age-related estimated maximum heart rate. Patients are advised not to exceed the recommended exercise duration or intensity. Duration 12 weeks. Concurrent medication/care: those receiving current treatment from a psychiatrist, psychologist, community psychiatric nurse, physiotherapist, or exercise therapist were excluded. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (design for CFS but unclear whether physiotherapists were specialised in CFS).
Funding	Other (Linbury Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus GET

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Chalder fatigue scale at average 3 and 8 month follow up scores ; Group 1: mean 17.56 (SD 6.78); n=15, Group 2: mean 20.02 (SD 7.9); n=21; Chalder fatigue scale 0-33 Top=High is poor outcome; Comments: baseline values (CFS group overall): 28.24 (4.54)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: baseline details not reported separately for CFS group (entire study sample only); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at longest follow up available; General symptom scales at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available;

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	Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Rimes 2013[635]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=37)
Countries and setting	Conducted in United Kingdom; Setting: Specialist NHS CFS unit
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 months (2 months intervention + 6 months follow-up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed as having CFS according to Fukuda 1994 or Oxford criteria at initial assessments.
Stratum	adults; severity mixed or unclear: Adults; score of ≥4 on Chalder fatigue scale (bimodal scoring), no further info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Adults; completed CBT program at a NHS CFS unit in the previous year; diagnosed as having CFS according to Fukuda 1994 and Oxford criteria at initial assessment; score of ≥4 on Chalder fatigue scale (bimodal scoring)
Exclusion criteria	Deemed to be unsuitable for group intervention; current major depression (stable dose antidepressant allowed if not currently meeting diagnostic criteria for major depression)
Recruitment/selection of patients	Participants were recruited from a specialist NHS CFS unit
Age, gender and ethnicity	Age - Mean (SD): MBCT 41.4 (10.9) years; control 45.2 (9.4). Gender (M:F): 6/29. Ethnicity: MBCT/control (%): white UK 93.8/63.2; white other 6.2/26.3; black African 0/5.3; other 0/5.3
Further population details	All participants had already completed a CBT program at a specialist NHS CFS unit.

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Extra comments	Other baseline characteristics, MBCT/control: in paid employment n=7/8; higher educational qualification n=13/12; duration of CFS symptoms in years, mean (SD) 8.5 (4.4)/6.1 (4.8); antidepressant medication n=5/5
Indirectness of population	Serious indirectness: 1994 CDC/Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=18) Intervention 1: Psychological and behavioural interventions - mindfulness. Mindfulness based cognitive course (MBCT), consisting of an introductory session, followed by 8 weekly sessions lasting 2.25hrs each. Followed Segal et al 2002 MBCT manual. Classes included mindfulness meditation practices which were also undertaken at home, usually with the support of CDs. In each class patients could talk about their experiences with mindfulness practice, issues and how to deal with them. Each class was organised around a theme that was explored through group inquiry and mindfulness practice. Programme adapted so that psycho-educative and cognitive components were consistent with a cognitive-behavioural model of CFS rather than depression. Intervention aimed at helping participants to become more aware of and relate differently to their thoughts, feelings, bodily sensation and self, including development of metacognitive awareness and a more accepting, non-judgmental compassionate attitude. Intended to help individuals disengage from unhelpful cognitive and behavioural reactions that may be maintaining symptoms/impairment/distress, and to develop new ways of coping. Participants were offered a 2 month follow-up class. Classes led by 2 clinical psychologists. Duration 2 months. Concurrent medication/care: antidepressant medication use n=5. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (Classes led by 2 clinical psychologists who met requirements of the Good Practice Guidance for Teaching Mindfulness-based Courses, and were supervised separately by experienced mindfulness instructors. Intervention took place at specialist CFS unit, but it is not clear if instructors were experienced CFS practitioners). (n=19) Intervention 2: no treatment. Participants in the wait-list control group were informed that their own MBCT group with start at the 2 month follow-up (4 months from start of study). Duration 2 months. Concurrent medication/care: antidepressant medication use n=5. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable

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Funding	Academic or government funding (UK Department of Health - National Institute for Health Research Biomedical Research Centre and Maudsley NHS Foundation Trust and the Institute of Psychiatry, King's College London)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINDFULNESS BASED COGNITIVE COURSE (MBCT) versus WAIT-LIST CONTROL

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue scale - total score at 4 months (2 months post-treatment); Group 1: mean 21.3 (SD 6.2); n=15, Group 2: mean 25 (SD 6.1); n=19; Chalder fatigue scale 11-item 0-33 Top=High is poor outcome; Comments: Baseline scores, mean (SD): MBCT 25.4 (5.1); control 23.4 (3.9)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, ethnicity, employment status, education, duration of CFS symptoms, antidepressant use, and baseline scores. ; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 3, Reason: n=1 did not receive intervention (withdrew due to family illness), n=1 withdrew after 1 session (did not like group nature of intervention), n=1 unclear; Group 2 Number missing: 0, Reason: NA

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Physical functioning-10 scale (PF-10) at 4 months (2 months post-treatment); Group 1: mean 65.6 (SD 26.3); n=16, Group 2: mean 55.9 (SD 23.3); n=19; Physical functioning scale (PF-10) 0-100 Top=High is good outcome; Comments: Baseline scores, mean (SD): MBCT 61.6 (22.7); control 55.5 (23.6)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, ethnicity, employment status, education, duration of CFS symptoms, antidepressant use, and baseline scores. ; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 2, Reason: n=1 did not receive intervention (withdrew due to family illness), n=1 withdrew after 1 session (did not like group nature of intervention); Group 2 Number missing: 0, Reason: NA

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression subscale at 4 months (2 months post-treatment); Group 1: mean 5.6 (SD 2.9); n=16, Group 2: mean 7.7 (SD 4.6); n=19; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores, mean (SD): MBCT 6.6 (4.4); control 7.9 (4.6)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age,

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gender, ethnicity, employment status, education, duration of CFS symptoms, antidepressant use, and baseline scores. ; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 2, Reason: n=1 did not receive intervention (withdrew due to family illness), n=1 withdrew after 1 session (did not like group nature of intervention); Group 2 Number missing: 0, Reason: NA
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety subscale at 4 months (2 months post-treatment); Group 1: mean 7.8 (SD 3.6); n=16, Group 2: mean 8.9 (SD 5.2); n=19; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores, mean (SD): MBCT 8.1 (4.7); control 8.3 (5.0)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, ethnicity, employment status, education, duration of CFS symptoms, antidepressant use, and baseline scores. ; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 2, Reason: n=1 did not receive intervention (withdrew due to family illness), n=1 withdrew after 1 session (did not like group nature of intervention); Group 2 Number missing: 0, Reason: NA

Protocol outcome 4: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Substantive adverse events at Unclear; Group 1: 0/18, Group 2: 0/19
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Authors reported no 'substantive' adverse events. Not further defined. Number of participants included/time point measured not clear. ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, ethnicity, employment status, education, duration of CFS symptoms, antidepressant use, and baseline scores. ; Blinding details: Blinding should not affect objective outcome; Group 1 Number missing: , Reason: n=1 did not receive intervention (withdrew due to family illness), n=1 withdrew after 1 session (did not like group nature of intervention); Group 2 Number missing: , Reason: No dropouts

Protocol outcome 5: Return to school or work at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Work and social adjustment scale at 4 months (2 months post-treatment); Group 1: mean 20 (SD 10.4); n=16, Group 2: mean 25.8 (SD 6.7); n=19; Work and social adjustment scale 0-40 Top=High is poor outcome; Comments: Baseline scores, mean (SD): MBCT 23.4 (9.1); wait-list 24.7 (8.0)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, ethnicity, employment status, education, duration of CFS symptoms, antidepressant use, and baseline scores. ; Blinding details: Subjective patient reported outcome; Group 1 Number missing: 2, Reason: n=1 did not receive intervention (withdrew due to family illness), n=1 withdrew after 1 session (did not like group nature of intervention); Group 2 Number missing: 0, Reason: NA

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Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study	Sharpe, 1996 trial: Sharpe 1996[678]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in United Kingdom; Setting: Hospital infectious diseases outpatient clinic
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Had to meet Oxford criteria for CFS; full history and psychiatric diagnostic interview completed to determine eligibility for inclusion.
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	The inclusion criteria specified that patients had to meet the "Oxford" criteria for the chronic fatigue syndrome.' Specifically they had to have (a) a principal complaint of fatigue exacerbated by physical or mental activity, or both, of six months' duration; (b) impairment of daily activities (Karnofsky score < 80; see below); and (c) no clinically significant findings on physical examination or laboratory investigation (full blood count, C reactive protein concentration, biochemical measurements, and thyroxine and thyroid stimulating hormone concentrations).
Exclusion criteria	Patients were excluded if they (a) were currently receiving psychotherapy or antidepressant drugs (unless they had been taking the same dose for at least three months without improvement); (b) were un- willing to accept randomisation or were unavailable for follow up; (c) met criteria for severe depression (melancholia) or had a history of bipolar affective disorder, schizophrenia, or substance misuse; or (d) were at significant risk of suicide or in need of urgent psychiatric treatment.

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Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): CBT 34 (9.1), standard medical care 38 (11.8) years. Gender (M:F): 19:41. Ethnicity: unclear
Further population details	-
Extra comments	CBT/SMC 34/38; married or cohabiting 63%/47%; education after 18 years 50%/73%; not working or studying 87%/50%; member of patient group 40%/43%; reported infection at onset 67%/73%; duration illness 17/20 months; disability on Karnofsky scale 71/72; major depressive disorder 20%/20%; any depressive disorder 53%/57%; any anxiety disorder 47%/50%; any anxiety or depression diagnosis 67%/67%; somatization disorder 10%/10%; percentage interference with activities 65%/64%; number of days in bed/week 3.3/1.6; 6 min walk distance 424m/435m; fatigue severity (out of 10) 7.8/7.9; HADS depression 6.7/6.8; HADS anxiety 6.3/8.4; belief that illness mainly physical 83%/73%; belief in avoidance of exercise 97%/83%.
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=30) Intervention 1: Psychological and behavioural interventions - CBT. Medical care plus cognitive behaviour therapy - in addition to the medical care outlined for the control group, patients given cognitive behaviour therapy were invited to attend 16 one hour individual treatment sessions over four months. The treatment had a cognitive emphasis and was tailored for patients with the chronic fatigue syndrome. It was administered by three experienced therapists. Therapy was codified in a manual and supervised by an experienced cognitive therapist. During treatment patients were encouraged to question a simple disease explanation of the illness and to consider the role of psychological and social factors. They were also invited to evaluate the effect of gradual and consistent increases in activity and to try strategies other than avoidance. Additional components of the treatment included strategies to reduce excessive perfectionism and self-criticism and an active problem-solving approach to interpersonal and occupational difficulties. Duration 4 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: tailored for patients with the chronic fatigue syndrome; unclear whether therapists were experienced/specialised in ME/CFS (n=30) Intervention 2: usual care - standard medical care. Medical care alone - Patients randomised to

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	receive medical care alone were reassured that there was no evidence of serious organic disease, told that they had the chronic fatigue syndrome, and advised to increase their level of activity by as much as they felt able. No further specific explanation or advice was given. Patients were followed up by their general practitioners in the usual way. Duration 4 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. type of intervention: not applicable
Funding	Academic or government funding (Wellcome Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus STANDARD MEDICAL CARE

Protocol outcome 1: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS anxiety at 12 months; MD; -0.3 (95%CI -2.2 to 1.6, Comments: MD of change from baseline, so a negative score denotes benefit to CBT. The paper reports positive values for this variable (as they are just expressing the difference), but their data shows that the findings are actually negative.);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differed in age but comparable for outcomes and for most demographic variables; Group 1 Number missing:; Group 2 Number missing: 1 missing and last values carried forward, but unclear from which group
- Actual outcome for adults; severity mixed or unclear: HADS depression at 12 months; MD; -2 (95%CI -4.1 to 0, Comments: MD of change from baseline, so a negative score denotes benefit to CBT. The paper reports positive values for this variable (as they are just expressing the difference), but their data shows that the findings are actually negative.);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differed in age but comparable for outcomes and for most demographic variables; Group 1 Number missing:; Group 2 Number missing: 1 missing and last values carried forward, but unclear from which group

Protocol outcome 2: Activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Percentage interference with activities at 12 months; MD; -14 (95%CI -25 to -3, Comments: MD of change from baseline, so a negative score denotes benefit to CBT. The paper reports positive values for this variable (as they are just expressing the difference), but their data shows that the findings are actually negative.);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differed in age but comparable for outcomes and for most demographic variables; Group 1 Number missing:; Group 2 Number missing: 1 missing and last values carried forward, but unclear from which group

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- Actual outcome for adults; severity mixed or unclear: Number of days in bed per week at 12 months; MD; -2.8 (95%CI -4 to -1.7, Comments: MD of change from baseline, so a negative score denotes benefit to CBT. The paper reports positive values for this variable (as they are just expressing the difference), but their data shows that the findings are actually negative.); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differed in age but comparable for outcomes and for most demographic variables; Group 1 Number missing:; Group 2 Number missing: 1 missing and last values carried forward, but unclear from which group Protocol outcome 3: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: 6 min walk distance at 12 months; MD; 55 (95%CI 17 to 94, Comments: MD of change from baseline, so a positive score denotes benefit to CBT.); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Differed in age but comparable for outcomes and for most demographic variables; Group 1 Number missing: 3; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Return to school or work at longest follow up available

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Study (subsidiary papers)	SMILE trial: Crawley 2018[204] (Anon 2019[549], Crawley 2013[201])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosed with 'CFS/ME' after a thorough assessment which included screening for other disorders associated with fatigue
Stratum	Children and young people; moderate severity: 12-18 year olds; diagnosed with ME/CFS; those too severely affected to attend hospital appointments were excluded; allocation to trial arms in equal proportions using minimization by age 12-15 and 16-18 years
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Children with 'CFS/ME'; between 12 and 18 years old inclusive
Exclusion criteria	Too severely affected to attend hospital appointments (defined as children and young people that do not regularly leave their house); or if they or their parents have insufficient English to either understand the patient information sheet and consent form to take part in the LP or the research interviews
Recruitment/selection of patients	Participants recruited after clinical assessment by the Bath/Bristol paediatric 'CFS/ME' service, a large regional and national NHS specialist service
Age, gender and ethnicity	Age - Mean (SD): intervention 14.7 (1.4), control 14.5 (1.6) years. Gender (M:F): 24/76. Ethnicity: British

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Further population details	-
Indirectness of population	No indirectness: NA
Interventions	(n=51) Intervention 1: Psychological and behavioural interventions - Lightning Process. Specialist medical care + Lightning Process: asked to read information about LP and complete an assessment form with their parents to identify their goals and describe what they had learnt. They then had a telephone call with an LP practitioner to discuss attending an LP course consisting of three 4-hour sessions on consecutive days run with groups of two to five young people. Each had a theory session with taught elements on the stress response, how the mind and body interact, and how thought processes can be either helpful or negative. This was followed by group discussion where the language used was discussed and in some cases challenged, and where participants were encouraged to think about what they could take responsibility for and change. In the practical session, participants identified a goal they wished to achieve (such as standing for longer) and were given different cognitive (thinking) strategies before and while the goal was attempted. They were also asked to identify a goal to attempt at home. After the course, young people were offered at least two follow-up phone calls with an LP practitioner. Duration approx. 4.5 months. Concurrent medication/care: Specialist medical care: focused on improving sleep and using activity management to establish a baseline level of activity (school, exercise and social activity) which is then gradually increased. Sessions were delivered by a range of trained and supervised professionals including doctors, psychologists, physiotherapists and occupational therapists in family-based rehabilitation consultations. Follow-up sessions were either face to face or by telephone. The number and timing of the sessions were agreed with the family depending on each adolescent's needs and goals. Those with significant anxiety or low mood were offered additional CBT. Participants could choose to use physiotherapist-delivered graded exercise therapy, which provides detailed advice about exercise and focuses on an exercise programme rather than other activities. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: unclear whether therapists were experienced/specialised in ME/CFS (n=49) Intervention 2: usual care - standard medical care. Specialist medical care: focused on improving sleep and using activity management to establish a baseline level of activity (school, exercise and social activity) which is then gradually increased. Sessions were delivered by a range of trained and supervised professionals including doctors, psychologists, physiotherapists and occupational therapists in family-based rehabilitation consultations. Follow-up sessions were either face to face or by telephone. The number and

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	timing of the sessions were agreed with the family depending on each adolescent's needs and goals. Those with significant anxiety or low mood were offered additional CBT. Participants could choose to use physiotherapist-delivered graded exercise therapy, which provides detailed advice about exercise and focuses on an exercise programme rather than other activities. Duration approx. 4.5 months. Concurrent medication/care: NA. No indirectness; Indirectness comment: NA Further details: 1. type of intervention: not applicable
Funding	Other (Linbury Trust; Ashden Trust; authors funded by NIHR)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LIGHTNING PROCESS versus STANDARD MEDICAL CARE

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for Moderate; age mixed or unclear: Chalder Fatigue score at 12 months; MD; -4 (95%CI -7.2 to 0.7) (p value : 0.017) Chalder Fatigue Scale 0-33 Top=High is poor outcome, Comments: Baseline values: intervention 25 (4.2), control 25.1 (4.2)
Mean difference adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).
n=74;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 9, Reason: unclear; Group 2 Number missing: 11, Reason: unclear

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for Moderate; age mixed or unclear: SF36 physical function at 12 months; MD; 18.6 (95%CI 6.9 to 30.4) (p value: 0.002) SF36 physical function 0-100 Top=High is good outcome, Comments: Baseline values: intervention 53 (18.8), control 56 (21.5)
Difference in means adjusted for age, gender, baseline outcome, baseline Spence Children's Anxiety Scale and Visual Analogue Scale
n=73;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 7, Reason: 2 not followed up, 1 followed up outside permitted time window, 3 withdrawn consent, 1 missing SF36 physical function at baseline; Group 2 Number missing: 12, Reason: 9 not followed up, 1 followed up outside permitted time window, 2 withdrawn consent

Protocol outcome 3: Psychological status at longest follow up available

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- Actual outcome for Moderate; age mixed or unclear: Spence Children's Anxiety Scale at 12 months; MD; -14.5 (95%CI -22.4 to 6.7) (p value : <0.001) Spence Children's Anxiety Scale 0-114 Top=High is poor outcome, Comments: Baseline values: intervention 29.8 (16.9), control 40.3 (20.1)
mean difference adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).
n=52;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 20, Reason: unclear; Group 2 Number missing: 22, Reason: unclear
- Actual outcome for Moderate; age mixed or unclear: Hospital Anxiety and Depression Scale - anxiety at 12 months; MD; -2.6 (95%CI -4.7 to 0.4) (p value: 0.019) HADS anxiety 0-21 Top=High is poor outcome, Comments: Baseline values: intervention 8.8 (4.5), control 10.4 (4.4)
mean difference adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).
n=53;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 22, Reason: unclear
- Actual outcome for Moderate; age mixed or unclear: Hospital Anxiety and Depression Scale - depression at 12 months; MD; -1.8 (95%CI -3.4 to 0.1) (p value : 0.037) HADS depression 0-21 Top=High is poor outcome, Comments: Baseline values: intervention 7.5 (3.1), control 8.1 (4.4)
mean difference adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).
n=53;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 18, Reason: unclear; Group 2 Number missing: 22, Reason: unclear

Protocol outcome 4: Pain at longest follow up available
- Actual outcome for Moderate; age mixed or unclear: Pain VAS at 12 months; MD; -6.5 (95%CI -19.4 to 6.5) (p value : 0.321)
Pain VAS not reported, assumed to be 0-100 Top=High is poor outcome, Comments: Baseline values: intervention 51.6 (28.5), control 42.4 (29.4)
Mean difference adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).
n=54;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 19, Reason: unclear; Group 2 Number missing: 22, Reason: unclear

Protocol outcome 5: Return to school or work at longest follow up available

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- Actual outcome for Moderate; age mixed or unclear: School/college attendance in the previous week at 12 months; MD; 1 (95%CI 0.2 to 1.8) (p value : 0.012) days, Comments: Baseline school attendance in previous week
- intervention: none 12%, 0.5 days 10%, 1 day 6%, 2 days 16%, 3 days 24%, 4 days 24%, 5 days 8%
- control: none 14.3%, 0.5 days 14.3%, 1 day 6.1%, 2 days 16.3%, 3 days 24.5%, 4 days 18.4%, 5 days 6.1%
Mean difference adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).
n=65;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the control group had a higher mean SCAS at baseline, although this was adjusted for in the analysis; Group 1 Number missing: 17, Reason: unclear; Group 2 Number missing: 13, Reason: unclear

Protocol outcome 5: Adverse events at longest follow up available
- Actual outcome for Moderate; age mixed or unclear: Serious adverse events attributable to study intervention at 12 months; Group 1 (n=39): 0 events; Group 2 (n=46); Comments: The exact number of participants in whom adverse events were measured was not reported as this data was reported only as a statement “Participants in the SMILE trial did not have any serious adverse events attributable to either treatment arm.” Numbers used in analysis are the numbers of participants reported to have received the intervention.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Group 1 Number missing: 7, Reason: unclear; Group 2 Number missing: 12, Reason: The number of participants missing are those not included in primary analysis at 12 months (lost to follow-up, consent withdrawn). Unclear if this applies to AE data or if all participants included in study/who received the intervention were assessed for AEs.

Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study	Soderberg 2001[691]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=14)
Countries and setting	Conducted in Sweden; Setting: unclear
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: diagnosed according to CDC criteria, no further details
Stratum	adults; severity mixed or unclear: age range 28 - 52 years; diagnosed according to CDC criteria, no further details regarding severity reported
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	women diagnosed with CFS according to the CDC criteria
Exclusion criteria	patients diagnosed as also having fibromyalgia
Recruitment/selection of patients	women diagnosed at the Clinic for Infectious Diseases were offered to participate, no further detail
Age, gender and ethnicity	Age - Median (range): 44.5 (28-52) years. Gender (M:F): all female. Ethnicity: not reported
Further population details	-
Extra comments	duration of symptoms 1.5-6.5 years; 9/14 had sudden onset

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Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=7) Intervention 1: Psychological and behavioural interventions - counselling. Focused group therapy: supportive and goal-oriented short-term therapy, 10 sessions of 1.5 hours each. Goal to promote ability to deal with sickness and life situation by working with issues such as acceptance of the new life situation, setting realistic levels of ambition and reflecting on connection between achievement/self-esteem and activity/rest. Content, theme and group dynamics were noted each session. Led by a psychologist. Duration 10 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (n=7) Intervention 2: no treatment. waiting list. Duration 5 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GROUP THERAPY versus WAITING LIST

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Gothenburg Quality of Life Scale at 5 months; Group 1: mean 62.9 (SD 18); n=7, Group 2: mean 64.6 (SD 10.8); n=6; Gothenburg Quality of Life Scale 18-126 Top=High is good outcome; Comments: Baseline values: group therapy 62.3 (17.4), waiting list 67.4 (10.1)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: group baseline demographics/characteristics not reported; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: not reported

-Actual outcome for adults; severity mixed or unclear: VAS Quality of Life Scale at 5 months; Group 1: mean 4.4 (SD 2.8); n=7, Group 2: mean 3.1 (SD 1.5); n=6; VAS 0-10 Top=High is good outcome; Comments: Baseline values: group therapy group therapy 3.3 (1.8), waiting list 3.3 (2.2)

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Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: group baseline demographics/characteristics not reported; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: not reported	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Stulemeijer 2005[716] (Knoop 2007[411], Knoop 2007[413])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=71)
Countries and setting	Conducted in Netherlands; Setting: department of child psychology
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC criteria, assessed by means of a detailed history and physical and laboratory examinations
Stratum	Children and young people, severity mixed or unclear: age range 10-17 years; meeting CDC (Fukuda 1994) criteria; severe fatigue and severe functional impairment defined as a score of 40 or more on the fatigue severity subscale of the checklist individual strength and a weighted score of 65 or less on the SF-36 physical functioning subscale
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Between 10 and 17.2 years of age (to allow the older participants to complete therapy before their 18th birthday) and met the US Centres for Disease Control Prevention criteria for chronic fatigue syndrome
Exclusion criteria	Psychiatric comorbidity, as assessed during an interview with both patients and parents by an experienced child psychologist
Recruitment/selection of patients	All consecutive patients with a major complaint of fatigue referred to the paediatrics outpatient clinic during the recruitment period were assessed for eligibility
Age, gender and ethnicity	Age - Mean (SD): CBT 15.6 (1.3), waiting list 15.7 (1.3) years. Gender (M:F): 7/62. Ethnicity: not reported

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Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=36) Intervention 1: Psychological and behavioural interventions - CBT. 10 individual sessions over five months. 2 treatment protocols adapted for 2 different patterns of physical activity: active and passive. For relatively active patients' treatment started with learning to recognise and accept their current state of fatigue and impairment. Subsequently, they reduced their levels of activity and learnt to respect the limitations. After achieving this balance, the patient started to build up activity levels. For passive patients a systematic programme of activity building was started as soon as possible. To assure adherence, beliefs that activity would aggravate symptoms were addressed and challenged. Parents were actively involved in supporting their child, parents' beliefs and behaviours regarding the condition of their child were explored and addressed. Aims of therapy took into account the specific developmental tasks of adolescents. In children younger than 15 years, parents often acted as a coach; for older participants, parents had to step back and encourage their child to take responsibility for the treatment. Return to full time education was always a goal of treatment, and a plan for returning to school was discussed early with everyone involved. Four child therapists who were trained and supervised by an experienced cognitive behavioural therapist administered all therapy. Duration 5 months. Concurrent medication/care: Patients assigned to immediate therapy had to agree to not having any further medical examinations or other treatments for fatigue during therapy. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (CBT for CFS, but unclear whether child therapists had experience/expertise in CFS). (n=35) Intervention 2: usual care - standard medical care. waiting list - free to have other examinations or treatments and informed beforehand that, if desired, they could start therapy directly after the second assessment. Duration 5 months. Concurrent medication/care: NA. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Other (Foundation for Children's Welfare Stamps Netherlands (Stichting Kinderpostzegels Nederland) and the ME Society (ME Stichting).

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus WAITING LIST

Protocol outcome 1: General symptom scales longest follow up available
- Actual outcome for Severity and age mixed or unclear: Self rated improvement completely recovered or much better at 5 months; Group 1: 25/35, Group 2: 15/34; Comments: Options were completely recovered, felt much better, had the same complaints, or had become worse than at the previous assessment
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline characteristics or outcome measures; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1)

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Checklist Individual Strength - fatigue severity sub scale at 5 months; Group 1: mean 30.2 (SD 16.8); n=35, Group 2: mean 44 (SD 13.4); n=34; Checklist Individual Strength fatigue severity sub scale 8-56 Top=High is poor outcome; Comments: Baseline values: CBT 52.5 (3.8), waiting list 51.6 (4.4)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline characteristics or outcome measures; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1)

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for Severity and age mixed or unclear: SF36 physical functioning at 5 months; Group 1: mean 69.4 (SD 28); n=35, Group 2: mean 55.3 (SD 21.1); n=34; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 42.1 (16.5), waiting list 45.3 (17)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline characteristics or outcome measures; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1)

Protocol outcome 4: Return to school or work at longest follow up available

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- Actual outcome for Severity and age mixed or unclear: School attendance (hours attended/total hours) at 5 months; Group 1: mean 74.7 hours (SD 37.8); n=35, Group 2: mean 66.7 hours (SD 36); n=34; Comments: Baseline values: CBT 46.2 (38.9), waiting list 56.4 (38.6)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant differences in baseline characteristics or outcome measures; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1)

Protocol outcome 4: Pain at longest follow up available
- Actual outcome for Severity and age mixed or unclear: Daily pain rating at 5 months; Group 1: mean -2.21 (SD 3.85); n=35, Group 2: mean -0.36 (SD 2.19); n=34; Comments: Baseline values not reported. Outcome definition - patients rated their pain on a daily self-observation list 4x/day during a period of 12 days, on a scale ranging from 0 (no pain) to 4 (very severe pain). The daily pain score could range between 0 and 16, and the total 12 daily pain scores were averaged into one daily observed pain (DOP) score. N=32 had pain symptoms daily or several times a week (60% muscle pain, 75% headache, 60% multi-joint pain, 19% sore throat).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the baseline scores were not reported so it is unclear if these were comparable between groups, other baseline characteristics were similar; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1). Imputation was used for missing data (last observation carried forward).

- Actual outcome for Severity and age mixed or unclear: Muscle pain at 5 months; Group 1: mean 2.4 (SD 1.0); n=35, Group 2: mean 2.7 (SD 0.8); n=34; Comments: Baseline value: CBT 2.7 (1.1), waitlist: 1.8 (0.9). Symptoms rated on 4 point Likert scale (never to every day), range 1 to 4.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: pain was lower in waitlist group at baseline, other characteristics similar; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1). Imputation was used for missing data (last observation carried forward).

- Actual outcome for Severity and age mixed or unclear: Multi-joint pain at 5 months; Group 1: mean 2.0 (SD 1.2); n=35, Group 2: mean 2.3 (SD 0.9); n=34; Comments: Baseline value: CBT 2.5 (1.2), waitlist: 2.6 (0.6). Symptoms rated on 4 point Likert scale (never to every day), range 1 to 4.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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	Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: baseline characteristics similar; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: 7, Reason: Excluded from trial (n=1), not starting therapy (n=3), withdrew (n=3); Group 2 Number missing: 2, Reason: Excluded from trial (n=1), withdrew (n=1). Imputation was used for missing data (last observation carried forward). Protocol outcome 5: Cognitive function at longest follow up available - Actual outcome for Severity and age mixed or unclear: Reaction time task – simple (ms) (change scores) at 5 months; Group 1: mean -30 (95% CI -53 to -8); n=35, Group 2: mean -18 (95% CI -41 to 4); n=34; Comments: Baseline values not reported. Assumed to be mean change score although this is not clearly reported. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the baseline scores were not reported so it is unclear if these were comparable between groups, other baseline characteristics were similar; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: unclear; Group 2 Number missing: unclear; 13 patients were missing follow-up data but it was not clear how many patients were missing from each group, and whether or not this was evenly distributed, reasons for missing data also unclear. Imputation was used for missing data (last observation carried forward). - Actual outcome for Severity and age mixed or unclear: Checklist individual strength – concentration subscale (change scores) at 5 months; Group 1: mean -30 (95% CI -53 to -8); n=35, Group 2: mean -18 (95% CI -41 to 4); n=34; Comments: Baseline values not reported. Assumed to be mean change score although this is not clearly reported. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: the baseline scores were not reported so it is unclear if these were comparable between groups, other baseline characteristics were similar; Blinding details: participants in the waiting list group could receive other treatments whereas this option was not available to CBT group; not reported how many/which treatments were used; Group 1 Number missing: unclear; Group 2 Number missing: unclear; 13 patients were missing follow-up data but it was not clear how many patients were missing from each group, and whether or not this was evenly distributed, reasons for missing data also unclear. Imputation was used for missing data (last observation carried forward).
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Psychological status at longest follow up available; Sleep quality at longest follow up available; adverse events at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study	Surawy 2005[722]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in United Kingdom; Setting: not reported
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: diagnosis methods not described
Stratum	adults; severity mixed or unclear: aged between 18 and 65; diagnosed with CFS and met Oxford criteria (no further detail on severity)
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients with a diagnosis of CFS following a thorough initial screening for infectious and physical diseases and who met the Oxford criteria
Exclusion criteria	Patients who did not have a primary diagnosis of CFS, were unable to travel to the group, or had a diagnosis of major depression or psychosis, were excluded.
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Range: 18-65 years. Gender (M:F): 8/10. Ethnicity: not reported
Further population details	-

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Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=9) Intervention 1: Psychological and behavioural interventions - mindfulness. Group mindfulness training programme based on mindfulness-based stress reduction and mindfulness based cognitive therapy each week. Duration 8 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: not stated/unclear (n=9) Intervention 2: usual care - standard medical care. Waiting list -received standard care that may have included visits to the GP and alternative therapies such as homeopathy or acupuncture, but not CBT or mindfulness. Duration 8 weeks. Concurrent medication/care: NA. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: not applicable
Funding	Other (Linbury Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GROUP MINDFULNESS TRAINING versus STANDARD MEDICAL CARE

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue scale at 8 weeks; Group 1: mean 18.56 (SD 8.13); n=9, Group 2: mean 20.38 (SD 8.26); n=8; Chalder fatigue scale 0-42 (not explicitly stated) Top=High is poor outcome; Comments: Baseline values: intervention 25.33 (6.24), control 21.25 (9.16)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: intervention group scored higher on Chalder fatigue scale at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: not possible to retrieve questionnaires

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 8 weeks; Group 1: mean 40 (SD 16.78); n=9, Group 2: mean 36.5 (SD 27.61); n=8; SF36 physical function 0-100 Top=High is good outcome; Comments: Baseline values: intervention 40.56 (22.56), control 42.5 (27)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: intervention group scored higher on Chalder fatigue scale at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: not possible to retrieve questionnaires

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Protocol outcome 3: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Hospital Anxiety and Depression Scale - anxiety at 8 weeks; Group 1: mean 8.22 (SD 2.99); n=9, Group 2: mean 8.63 (SD 4.57); n=8; HADS anxiety 0-21 Top=High is poor outcome; Comments: Baseline values: intervention 11.44 (4.56), control 9.13 (5.11) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: intervention group scored higher on Chalder fatigue scale at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: not possible to retrieve questionnaires - Actual outcome for adults; severity mixed or unclear: Hospital Anxiety and Depression Scale - depression at 8 weeks; Group 1: mean 8.33 (SD 1.66); n=9, Group 2: mean 9.5 (SD 3.96); n=8; HADS depression 0-21 Top=High is poor outcome; Comments: Baseline values: intervention 9 (4.58), control 10.5 (3.16) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: intervention group scored higher on Chalder fatigue scale at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 1, Reason: not possible to retrieve questionnaires	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Sutcliffe 2010[723]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in United Kingdom; Setting: primary care
Line of therapy	Unclear
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients diagnosed with CFS according to the Fukuda diagnostic criteria; unclear if diagnosis confirmed for the study.
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients 18 years and over diagnosed with CFS (Fukuda criteria) attending the 'CFS/ME' Clinical Service
Exclusion criteria	Inability to give informed consent; patients on drugs which can affect the autonomic nervous system that cannot b3e discontinued safely; inability to stand for up to 40 minutes due to muscular or neurological disorders, or pregnancy
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 48 (12). Gender (M:F): 7/31. Ethnicity: Not specified
Further population details	-

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Extra comments	Subjects were not selected negatively or positively by presence of autonomic symptoms or history of loss of consciousness.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=19) Intervention 1: Exercise interventions – Home orthostatic training (HOT). Participants were asked to stand with their upper back against a wall and their heels approximately 15 centimetres (cm) from the wall with a cushioned 'drop zone'. They were asked to maintain this position without movement for up to 40 minutes or until they experienced symptoms. Duration 6 months. Concurrent medication/care: All participants continued to receive routine clinical care. Indirectness: No indirectness Further details: 1. type of intervention: not stated/unclear (n=19) Intervention 2: placebo or sham - placebo/sham. Participants were asked to stand against a wall with their upper back against the wall and their heels approximately 15 cm from the wall with a cushioned 'drop zone'. They were also taught to perform gentle flexion and extension exercises with their calf muscles while standing against the wall, to enhance believability counter venous pooling and prevent any possible orthostatic training effect. Duration 6 months. Concurrent medication/care: All participants continued to receive routine clinical care. Indirectness: No indirectness Further details: 1. type of intervention: not applicable
Funding	Academic or government funding (study funded by the Northern Regional 'CFS/ME' Clinical Network; author supported by a Nuffield Foundation Vacation Bursary.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOME ORTHOSTATIC TRAINING (HOT) versus PLACEBO/SHAM

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue at 4 weeks of treatment; Group 1: mean 92.9 (SD 35.9); n=18, Group 2: mean 92.5 (SD 25.8); n=18
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Mean (SD) baseline FIS scores were 97.7 (24.7) vs 92.9 (25.8) for the placebo vs the HOT group respectively; Blinding details: Majority of patients in both groups did not identify correctly the treatment they had been allocated to; Group 1 Number missing: 1, Reason: patient decided to withdraw from the study before the 4 weeks assessment;

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Group 2 Number missing: 1, Reason: patient decided to withdraw from the study before the 4 weeks assessment	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Taylor 2004[732] (Taylor 2006[734])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in USA; Setting: center for independent living
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: screening process to confirm self-reported diagnosis of chronic fatigue syndrome: Chronic Fatigue Syndrome Screening Questionnaire to evaluate presence, frequency, and severity of chronic fatigue syndrome symptoms according to Fukuda 1994 criteria; Structured Clinical Interview for the DSM-IV administered by a licensed clinical psychologist to rule out psychiatric conditions that would exclude an individual from a chronic fatigue syndrome diagnosis; collection of past medical records documenting a diagnosis of chronic fatigue syndrome by a physician; and independent physician review of results from the Chronic Fatigue Syndrome Screening Questionnaire, the psychiatric interview, and the medical records to determine whether the potential participants met chronic fatigue syndrome criteria
Stratum	adults; severity mixed or unclear: 'adults'; meeting CDC criteria, no further details on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Adults meeting Fukuda criteria
Exclusion criteria	Exclusionary medical conditions; not meeting Fukuda criteria
Recruitment/selection of patients	Local chronic fatigue syndrome self-help organizations and physicians specializing in the treatment of people with chronic fatigue syndrome and advertisements posted in chronic fatigue syndrome newsletters local newspapers, on chronic fatigue syndrome Websites and Listservs, and on a local cable TV station

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Age, gender and ethnicity	Age - Mean (SD): programme 49 (10.9), waiting list 44.9 (9.7) years. Gender (M:F): 2/45. Ethnicity: minority n=8, non-minority n=39
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=23) Intervention 1: Psychological and behavioural interventions - pragmatic rehabilitation. Eight sessions of an illness-management group, biweekly over a period of 4 months, co-led by a peer counsellor and the author. The first part of each group session (hour 1) consisted of individual check-in and reporting on self-monitored goal attainment. In the second part of each group session (hour 2), participants participated in an educational lecture and discussion of self-selected, chronic fatigue syndrome-relevant topics. Group topics included activity pacing using the Envelope Theory, cognitive coping skills training, relaxation and meditation training, employment issues and economic self-sufficiency, personal relationships, traditional and complementary medical approaches, and nutritional approaches. Program developed using participatory action research, in which people with disabilities can take an active role in designing and conducting research. The structure and logistical elements were developed conjointly by members of the local self-help organization serving individuals with chronic fatigue syndrome, staff of the center for independent living, and researchers with expertise in the study of chronic fatigue syndrome. Duration 4 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (delivered by peer counsellor with CFS and developed in collaboration with participants). (n=23) Intervention 2: Psychological and behavioural interventions - counselling. Following the 4-month period of illness-management group sessions (part 1), immediate program participants received seven months of peer counselling, which consisted of self-advocacy training, continued monitoring of goal attainment, and ongoing case coordination services by one of the peer counsellors (part 2). Resource funds in the amount of $300 per participant were provided to each participant to support goal attainment, service acquisition, and local travel needs. In order to obtain the funds, participants were required to state how the financial expenditure would facilitate goal attainment and independent living. Duration 7 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA

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	Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (peer counsellors had CFS and counselling focused on CFS). (n=24) Intervention 3: no treatment. Delayed programme group. Duration 12 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (U.S. Department of Education National Institute on Disability and Rehabilitation Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ILLNESS MANAGEMENT GROUP + PEER COUNSELLING versus DELAYED PROGRAMME

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Quality of life index at 12 months; Group 1: mean 15.7 (SD 3.7); n=23, Group 2: mean 14.6 (SD 4.1); n=24; Quality of life index 0-30 Top=High is good outcome; Comments: Baseline values: programme 13.1 (4.3), waiting list 14 (3.9)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant sociodemographic differences or differences in outcome at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcome 2: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chronic Fatigue Syndrome Symptom Rating Form at 12 months; Group 1: mean 13.9 (SD 3.5); n=23, Group 2: mean 14.8 (SD 2.8); n=24; Chronic Fatigue Syndrome Symptom Rating Form 0-100 Top=High is poor outcome; Comments: Baseline values: programme 15.1 (3), waiting list 14.2 (2.8)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant sociodemographic differences or differences in outcome at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: CORE-E - overall resource gain at 12 months; Group 1: mean 81.82 (SD 75.78); n=23, Group 2: mean 53.29 (SD 47.78); n=24; CORE-E 0-518 Top=High is good outcome; Comments: Baseline scores, mean (SD): program 69.26 (60.28); 106.63 (88.55)
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

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- Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant sociodemographic differences or differences in outcome at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA - Actual outcome for adults; severity mixed or unclear: CORE-E - overall resource loss at 12 months; Group 1: mean 109.05 (SD 87.82); n=23, Group 2: mean 124.96 (SD 97.93); n=24; CORE-E 0-518 Top=High is poor outcome; Comments: Baseline scores, mean (SD): program 229 (98.26); control 222.13 (108.65) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: no significant sociodemographic differences or differences in outcome at baseline; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	The 2007[753]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=57)
Countries and setting	Conducted in Netherlands; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants met 1994 CDC criteria; psychiatric comorbidity was excluded by structured interview; no mention of physician diagnosis/physical examination, etc. 26% of participants recruited from outpatient department, 74% from ME patient organisation newsletter.
Stratum	adults; severity mixed or unclear: Adults age 18-65 years; patients with substantial functional impairment included - score >800 on SIP-8; score >35 on fatigue scale.
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Fulfilled 1994 CDC criteria; age 18-65 years; substantial functional impairment with score >800 on SIP-8; score >35 on fatigue scale
Exclusion criteria	Current psychiatric comorbidity; pregnant or lactating; patients taking psychotropic drugs or experimental medications.
Recruitment/selection of patients	Patients were recruited through a general internal medicine outpatient clinic (n=15) and through an advertisement in the newsletter of Dutch CFS patient organisation (n=42)
Age, gender and ethnicity	Age - Mean (SD): Acclydine 40.9 (9.4) years; placebo 43.4 (11.2) years. Gender (M:F): 18/39. Ethnicity:

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Further population details	-
Extra comments	No. of CDC symptoms, mean (SD): acclydine 7.6 (1.4); 7.5 (1.3).
Indirectness of population	Very serious indirectness: Study only included patients who had a IGFBP3/IGF1 ratio greater than 2.5 and 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=30) Intervention 1: dietary supplementation - acclydine and amino acids. Acclydine capsules manufactured by Optipharma. Each capsule contained 250mg of the alkaloid. Patients took a single daily dose on an empty stomach, with the following decreasing dosage schedule: weeks 1–2, 1,000mg/day; weeks 3–6, 750mg/day; weeks 7–8, 500mg/day; weeks 9–10, 500mg every 2 days; weeks 11–12, 250mg/day; and weeks 13–14, 250mg every 2 days. Acclydine treatment was combined with amino acid supplements to provide sufficient essential and nonessential amino acid intake during treatment. Duration 14 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=27) Intervention 2: placebo or sham - placebo/sham. Patients in the placebo group received placebo Acclydine and placebo amino acid supplements. There was no difference in taste, appearance, or packaging between the active supplements and the placebo capsules. Duration 14 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Study funded by industry (Optipharma, Susteren and Planet Vital, Maastricht-Airport)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACCLYDINE AND AMINO ACIDS versus PLACEBO ACCLYDINE AND PLACEBO AMINO ACIDS

Protocol outcome 1: General symptom scales at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness impact profile-8 (SIP-8) at 14 weeks; Group 1: mean 1228.1 (SD 619.7); n=30, Group 2: mean 1120.2 (SD 543); n=27; Sickness impact profile-8 0-5799 Top=High is poor outcome; Comments: Baseline scores, mean (SD): acclydine 1484 (520.4); placebo 1317 (481.7). Treatment effect (difference in change scores) (95% CI): 59.1 (-201.7, 319.8), p-value 0.65
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

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Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, CDC symptoms, baseline score. More females in Acclydine group (77% vs 59%); Blinding details: Placebo identical appearance, taste, packaging to active treatment; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist individual strength - fatigue severity subscale at 14 weeks; Group 1: mean 42.4 (SD 11.6); n=30, Group 2: mean 43 (SD 12.6); n=27; Checklist individual strength 8-56 Top=High is poor outcome; Comments: Baseline scores, mean (SD): acclydine 46.5 (7.4); placebo 46.2 (7.9). Treatment effect (difference in change scores) (95% CI): 1.1 (-4, 6.5), p value 0.7
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, CDC symptoms, baseline score. More females in Acclydine group (77% vs 59%); Blinding details: Placebo identical appearance, taste, packaging to active treatment; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 3: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Important side effects at 14 weeks; Group 1: 0/30, Group 2: 0/27; Comments: Reported as: Acclydine and placebo treatments were well tolerated. No important side effects were reported in either group.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Adverse events reported narratively in results section, not pre-specified in methods; study authors do not define what were considered 'important side effects'; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, CDC symptoms, baseline score. More females in Acclydine group (77% vs 59%); Blinding details: Placebo identical appearance, taste, packaging to active treatment. Participants, investigators and lab technicians blinded. Unclear who assessed outcome; Group 1 Number missing: unclear, Reason: n=1 dropped out (unclear if included); Group 2 Number missing: unclear, Reason: n=1 dropped out (unclear if included)

Protocol outcome 4: Activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Actometer at 14 weeks; Group 1: mean 64.9 Unclear (SD 23.4); n=30, Group 2: mean 64.9 (SD 23.5); n=27; Comments: Actometer worn continuously for 14 days during the assessment periods, the average score over 12 days was computed. Baseline scores, mean (SD): acclydine 60.8 (20.5); placebo 64.8 (25.2). Treatment effect (difference in change scores) (95% CI): 4.1 (-5.9, 14), p-value 0.42.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, CDC symptoms, baseline score. More females in Acclydine group (77% vs 59%); Blinding details: Placebo identical appearance, taste, packaging to active treatment; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

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Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Tummers 2012[769]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=123)
Countries and setting	Conducted in Netherlands; Setting: community-based mental health centre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC criteria; if diagnosis was doubtful, based on baseline assessment and/or referral letter, a CFS expert contacted the referring GP or consultant for additional information to evaluate whether the diagnosis CFS was justified. Eligibility was examined again during the 30-min intake session with the psychiatric nurse, who asked the patient about the presence of somatic or psychiatric conditions other than CFS. If they were present, the nurse contacted the researcher who informed the CFS expert. If necessary, the expert contacted the GP or consultant for additional information. If the diagnosis of CFS could be confirmed, the patient was included in the study.
Stratum	adults; severity mixed or unclear: aged between 18 and 65 years; CFS according to the US Centers for Disease Control and Prevention (CDC) criteria - severe fatigue defined as >35 on the sub-scale fatigue severity of the Checklist Individual Strength, severely disabled operationalized as scoring <70 on the physical and/or social functioning subscale of the Medical Outcomes Survey Short Form-36 - no further detail on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Aged between 18 and 65 years; CFS according to the US Centers for Disease Control and Prevention (CDC) criteria
Exclusion criteria	Engaged in a legal procedure concerning disability-related financial benefit

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Recruitment/selection of patients	All referred patients meeting eligibility criteria during recruitment period
Age, gender and ethnicity	Age - Mean (SD): intervention 36.3 (12.1), waiting list 36.4 (13.6) years. Gender (M:F): 27/96. Ethnicity: not reported
Further population details	-
Indirectness of population	Very serious indirectness: during the study, for 12 patients the diagnosis of CFS turned out to be incorrect: four patients had a possible somatic explanation for their fatigue (e.g. brain damage), and eight patients seemed to have a psychiatric co-morbidity, of whom two had a substance-related disorder. The 12 patients were equally distributed between the two conditions. None of these patients were excluded from analyses. 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=62) Intervention 1: Psychological and behavioural interventions - CBT. Guided self-instruction consisted of an information booklet about CFS and assignments. Patients could follow the programme, based on the protocol of CBT for CFS described in the booklet, week by week for 20 weeks. The programme challenges patients to establish goals, explains the precipitating and perpetuating factors, challenges fatigue-related cognitions and encourages to develop a sense of control over symptoms. Patients learn to reduce the focus on fatigue and establish a sleep routine. Relatively active patients (alternation of periods of (over)activity and periods of rest) first have to learn to divide their activities more evenly, then gradually increase physical activity level, by walking or riding a bicycle. Patients with a low-active physical activity pattern start immediately with gradually increasing their physical activity level. Beliefs that activity would exacerbate symptoms are challenged. Patients make a plan for work resumption, containing the date when a patient will resume work, and how they will increase the hours worked. Excessive expectations regarding the response of their social environment to their symptoms are modified and patients learn how to communicate about CFS. Patients gradually increase their mental and social activities, attain the goals as formulated earlier on step by step, including resumption of work. Finally, patients learn how to prevent a relapse and how to further improve self-control. Patients were asked to email once every 2 weeks to ask questions about the treatment and nurses monitored the progress. Intervention carried out by 8 psychiatric nurses trained in coaching patients with the minimal intervention (4 training sessions of 4 h). Nurses received 2-weekly supervision by a cognitive behavioural therapist experienced in CBT for CFS. Duration 20 weeks. Concurrent medication/care: advised to stop other treatments for fatigue. Indirectness: No

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	indirectness; Indirectness comment: NA Further details: 1. type of intervention: intervention delivered by experienced or specialist CFS practitioners specifically designed for ME/CFS (supervision by a cognitive behavioural therapist experienced in CBT for CFS and programme designed for CFS). (n=61) Intervention 2: no treatment. Waiting list. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Academic or government funding (Dutch Medical Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUIDED SELF-INSTRUCTION versus WAITING LIST

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual Strength fatigue severity at 6 months; MD; -8.1 (95%CI -12.4 to -3.8) (p value : <0.01) Checklist Individual Strength fatigue severity 8-56 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: No significant baseline demographic differences, or differences in outcome at baseline; Blinding details: intervention group advised to stop other fatigue treatments; Group 1 Number missing: 7, Reason: discontinued, did not want to complete second assessment; Group 2 Number missing: 5, Reason: discontinued, did not want to complete second assessment

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 6 months; MD; 7.37 (95%CI -0.9 to 15.65) (p value : 0.08) SF36 physical functioning 0-100 Top=High is good outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: No significant baseline demographic differences, or differences in outcome at baseline; Blinding details: intervention group advised to stop other fatigue treatments; Group 1 Number missing: 7, Reason: discontinued, did not want to complete second assessment; Group 2 Number missing: 5, Reason: discontinued, did not want to complete second assessment

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Symptom Inventory at 6 months; MD; -0.1 (95%CI -0.2 to 0.09) (p value : 0.3) Brief Symptom Inventory not reported Top=High is poor outcome;

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Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: No significant baseline demographic differences, or differences in outcome at baseline; Blinding details: intervention group advised to stop other fatigue treatments; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 9, Reason: unclear	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Wallman 2004[815]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Australia; Setting: Primary care
Line of therapy	Unclear
Duration of study	Other: 4 weeks before intervention, 12 weeks of intervention and 4 weeks after intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: written confirmation of a CFS diagnosis, as defined by Fukuda et al (CDC 1994 diagnostic criteria) was required from each subject's doctor.
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	'CFS' patients that were able to provide written confirmation of a CFS diagnosis, as defined by Fukuda et al (CDC 1994 diagnostic criteria) was required from each subject's doctor.
Exclusion criteria	alternative diagnoses, failure to provide written confirmation of diagnosis
Recruitment/selection of patients	CFS patients were recruited from notices placed in medical surgeries and by advertisements in local newspapers.
Age, gender and ethnicity	Age - Range: 16 to 74. Gender (M:F): Define. Ethnicity: Not specified
Further population details	-

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Extra comments	Six subjects were classified as having had a major depressive disorder in the previous 12 months (single episodes that ranged from mild to severe without psychotic features. Two subjects were classified with dysthymia.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=34) Intervention 1: Exercise interventions - GET. Initial exercise duration was between 5 and 15 minutes, and intensity was based on the mean HR value achieved mid-point during the sub-maximal exercise tests. Graded exercise consisted of an aerobic activity that used the major large muscles of the body, of either walking, cycling or swimming. Subjects were instructed to exercise every second day unless they had a relapse. If this occurred or if symptoms became worse, the next exercise session was shortened or cancelled and subsequent sessions were reduced to a length that subjects felt was manageable (pacing). Each subject was supplied with a small laminated Borg scale, and an HR monitor to help them reach and maintain their required HR goals. Subjects rated the effort of each exercise session and recorded their exercise details in a diary. They were contacted by phone every second week over the 12 weeks to review their progress and to determine their exercise regimen for the following fortnight. Duration 12 weeks. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: not specified/ unclear (n=34) Intervention 2: Relaxation techniques - relaxation techniques (i.e. Alexander technique). Subjects were required to listen to a relaxation tape, and perform selected stretching exercises every second day for 12 weeks. All subjects kept a diary recording their relaxation/flexibility sessions. They were contacted by phone every second week to review their progress and to discuss the flexibility regimen for the following fortnight. They had been specifically requested not to participate in any extra physical activity while they were enrolled in the study. The exercise physiologist attempted to spend the same amount of time on the phone with all subjects in both therapy groups. Duration 12 weeks. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: involved exercise physiologist
Funding	Other (not stated)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus RELAXATION/ FLEXIBILITY PROGRAM

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Self-rated global impression change at 4 weeks post intervention; Group 1: 19/32, Group 2: 12/29; Comments: No Of Events= number of people rating themselves as 1: 'very much better' or 2: 'much better', extracted as categorised in other studies including this outcome; although in the current paper the category for clinical improvement seems to also include people with a self-rating of 3: 'a little better' with 29/32 people in the exercise group vs 22/29 people in the relaxation/ flexibility group rating themselves as being better according to the study's classification system.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Mental fatigue at 4 weeks post intervention; Group 1: mean 4.5 (SD 2.02); n=32, Group 2: mean 4.8 (SD 1.92); n=29
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: difference in baseline scores; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

- Actual outcome for adults; severity mixed or unclear: Physical fatigue at 4 weeks post intervention; Group 1: mean 8.1 (SD 3.75); n=32, Group 2: mean 9.6 (SD 3.57); n=29; Chalder's fatigue scale 0-21 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Stroop test (82 questions) at 4 weeks post intervention; Group 1: mean 79.4 (SD 4.04); n=32, Group 2: mean 71.1 (SD 21.43); n=29; Comments: A computerised version of the modified Stroop Colour Word test was used. There were two levels of

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difficulty based on speed of presentation. The 82 question Stroop was the less difficult version of the test.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: difference in baseline scores; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

- Actual outcome for adults; severity mixed or unclear: Stroop test (95 questions) at 4 weeks post intervention; Group 1: mean 87.5 (SD 17.61); n=32, Group 2: mean 73.1 (SD 35.17); n=29; Comments: A computerised version of the modified Stroop Colour Word test was used. There were two levels of difficulty based on speed of presentation. The 95 questions Stroop was the more difficult version of the test.
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: difference in baseline scores; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Depression (HADS) at 4 weeks post intervention; Group 1: mean 4.8 (SD 3.17); n=32, Group 2: mean 6.5 (SD 3.02); n=29; Comments: score <8 is considered non-pathological; SDs calculated from confidence intervals reported
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

- Actual outcome for adults; severity mixed or unclear: Anxiety (HADS) at 4 weeks post intervention; Group 1: mean 5.7 (SD 4.04); n=32, Group 2: mean 7.8 (SD 3.85); n=29; Hads Anxiety and Depressions Scale (HADS) 0-21 Top=High is poor outcome; Comments: SDs calculated from confidence intervals
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline differences in anxiety scores with exercise group mean scores being lower than the cut-off score considered pathological and relaxation/flexibility group mean scores exceeding this cut-off; Blinding details: Not possible to blind participants and caregivers due to nature of interventions; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test

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Protocol outcome 5: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Oxygen uptake/VO2 peak (ml/kg/min) at 4 weeks post intervention (during exercise test); Group 1: mean 17.1 mL/kg/min (SD 6.06); n=32, Group 2: mean 14.4 mL/kg/min (SD 5.5); n=29; Comments: Means of mean values at target heart rate (THR) for participants who reached THR, and peak values for participants who did not reach THR in exercise test. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness; Blinding details: Lack of blinding unlikely to influence physiological scores; Group 1 Number missing: 2, Reason: reasons not associated with the study; Group 2 Number missing: 5, Reason: reasons not associated with the study; excluded because body mass index (44kg/m2) prevented patient from participating in the exercise test	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study	Wearden 1998[836]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in United Kingdom; Setting: university department of medicine out-patient clinic
Line of therapy	Unclear
Duration of study	Intervention + follow up: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients met Oxford research criteria for CFS and had been medically assessed by a doctor
Stratum	Adults; moderate severity
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 18 years, meeting Oxford research criteria for CFS; pre-menopausal women were required to take precautions against pregnancy during the trial; people taking anti-depressant medication were required to stop and undergo at least two weeks of washout period
Exclusion criteria	Not specified
Recruitment/selection of patients	Consecutive referrals
Age, gender and ethnicity	Age - Mean (SD): intervention: 40.4 (11.9); control: 37.6 (10.7). Gender (M:F): 20/48. Ethnicity: not specified
Further population details	-

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Extra comments	The population of the two arms extracted as intervention and control were part of a RCT that originally had four arms, two of which were relevant to exercise interventions and have hence been extracted in this review.
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Exercise interventions - GET. Participants were told they would receive one of two forms of lifestyle advice and were blind to the other type of advice; They were instructed to carry out their preferred aerobic activity (usually walking/jogging, swimming or cycling) for 20 minutes at least three times per week. The intensity of the activity was initially set at a level which utilised oxygen at approximately 75% of the subject's tested functional maximum. Subjects monitored their prescribed exercise programmes on a chart along with pre-and-post-exercise heart rates and perceived exertion. Exercise intensity was increased when there was a consistent recorded reduction of 10 beats per minute in post-exercise heart rate for one week and two points on the perceived exertion scale (about three times in six months in an adherent patient). Subjects adhered to the exercise programme if their charts showed that they had performed the required intensity, at least three times per week. Duration 26 weeks. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: not stated/unclear (n=34) Intervention 2: placebo or sham - placebo/sham. Subjects were not offered any specific advice on how much exercise they should be taking, but were told to do what they could when they felt capable and to rest when they felt they needed to. Subjects who attended the required appointments adhered to the non-exercise treatment. Duration 26 weeks. Concurrent medication/care: not specified. Indirectness: No indirectness Further details: 1. type of intervention: not applicable
Funding	Other (The Linbury Trust)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus PLACEBO/SHAM

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue at 26 weeks; Group 1: mean -5.7 (SD 11.3); n=34, Group 2: mean -2.7 (SD 8.06); n=34;

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Comments: ITT analysis with scores on previous assessment carried forward; SD calculated from 95% CIs reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - High; Indirectness of outcome: No indirectness; Baseline details: baseline differences in age, duration of fatigue at baseline could have influenced results; Group 1 Number missing: 11, Reason: 11 of those randomised (n=34) dropped out from treatment, and 23 fully completed all assessments and only 14 of those were assessed to comply fully with graded exercise; Group 2 Number missing: 5, Reason: 5 of those randomised (n=34) dropped out and 29 completed all assessments Protocol outcome 2: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Depression at 26 weeks; Group 1: mean -1.2 (SD 3.87); n=34, Group 2: mean -1.3 (SD 2.97); n=34; Comments: SDs calculated from 95% CIs Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - High; Indirectness of outcome: No indirectness; Baseline details: baseline differences in age, duration of fatigue at baseline could have influenced results; Group 1 Number missing: 11, Reason: 11 of those randomised (n=34) dropped out from treatment, and 23 fully completed all assessments and only 14 of those were assessed to comply fully with graded exercise; Group 2 Number missing: 5, Reason: 5 of those randomised (n=34) dropped out and 29 completed all assessments Protocol outcome 3: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Functional work capacity (fwc – VO2 peak) at 26 weeks; Group 1: mean 2.8 ml O2/kg/min (SD 5.95); n=34, Group 2: mean -0.1 ml O2/kg/min (SD 5.06); n=34; Comments: Outcome was determined using a Bosch ERG 551 electronically braked cycle ergometer. It was calculated as the amount of oxygen (in millilitres) consumed in the final minute of exercise per kilogram of body weight. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - High; Indirectness of outcome: No indirectness; Baseline details: baseline differences in age, duration of fatigue at baseline could have influenced results; Group 1 Number missing: 11, Reason: 11 of those randomised (n=34) dropped out from treatment, and 23 fully completed all assessments and only 14 of those were assessed to comply fully with graded exercise; Group 2 Number missing: 5, Reason: 5 of those randomised (n=34) dropped out and 29 completed all assessments	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available

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Study	Weatherley-Jones 2004[838]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=103)
Countries and setting	Conducted in United Kingdom; Setting: Two community homeopathy clinics
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients included if they met the Oxford criteria for CFS diagnosis. Physical examination, blood tests, and a psychiatric assessment performed as part of assessment for eligibility.
Stratum	adults; severity mixed or unclear: Age >18 years and meeting the Oxford criteria - no further information on severity.
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Age >18 years; meeting the Oxford criteria for CFS case definition; no clinically significant abnormalities in full blood count, liver function tests, thyroid stimulating hormone, acute phase protein, urea and electrolytes, and no protein or glucose in urine.
Exclusion criteria	Psychiatric exclusions: primary major depression, bipolar disorders, psychosis, eating disorders, substance abuse/dependence, somatisation disorders; currently engaged in individual counselling or psychotherapy; in clinical trials for other CFS treatments; already receiving or completed homeopathic treatment or CBT for CFS; pregnant.
Recruitment/selection of patients	Patients were recruited from two hospital outpatient clinics. Consecutive new referrals were assessed for eligibility.

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Age, gender and ethnicity	Age - Mean (SD): homeopathy group 38.9 (10.6) years; placebo group 38.8 (11.2) years. Gender (M:F): 42/61. Ethnicity: Not reported
Further population details	-
Extra comments	-
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=53) Intervention 1: complementary therapies - homeopathy. Monthly consultations with a registered homeopath (9 homeopaths from 2 clinics); 90 minutes for initial consultation and 45 minutes for subsequent consultations. Homeopaths prescribed remedies according to their usual practice, generally a single remedy per consultation. Remedy prepared/dispensed by single homeopathic pharmacy. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (n=50) Intervention 2: placebo or sham - placebo/sham. Monthly consultations with a registered homeopath (9 homeopaths from 2 clinics); 90 minutes for initial consultation and 45 minutes for subsequent consultations. Homeopaths prescribed remedies according to their usual practice, generally a single remedy per consultation. Placebos were prepared in the same way as the homeopathic medicines, but did not contain the indicated source material. Placebo prepared/dispensed by single homeopathic pharmacy. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear
Funding	Other (Grant from a charitable trust (Linbury Trust))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOMEOPATHIC MEDICINE versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Functional limitations profile - physical dimension at 7 months; Group 1: mean 5.11 (SD 8.82); n=43, Group 2: mean 2.72 (SD 8.4); n=43; Functional limitations profile Not reported Top= High is poor outcome; Comments: It is unclear if these are

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mean percentage changes or absolute changes in score. ANCOVA analysis with baseline outcome value as covariate.
Baseline scores (SD): homeopathic medicine 20.4 (14.1); placebo 22.1 (14.9).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Functional limitations profile - psychosocial dimension at 7 months; Group 1: mean 9.81 (SD 14.19); n=43, Group 2: mean 6.76 (SD 10.67); n=43; Functional limitations profile Not reported Top= High is poor outcome; Comments: It is unclear if these are mean percentage changes or absolute changes in score. ANCOVA analysis with baseline outcome value as covariate.
Baseline scores (SD): homeopathic medicine 35.1 (14.8); placebo 36.3 (15.0).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - general fatigue at 7 months; Group 1: mean 2.7 (SD 3.93); n=43, Group 2: mean 1.35 (SD 2.66); n=43; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline scores (SD): homeopathic medicine 18.4 (1.7); placebo 18.1 (2.2).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data

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from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - physical fatigue at 7 months; Group 1: mean 2.13 (SD 4); n=43, Group 2: mean 1.28 (SD 2.74); n=43; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline scores (SD): homeopathic medicine 18.0 (2.2); placebo 17.5 (3.1).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers reported missing reflects excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - mental fatigue at 7 months; Group 1: mean 2.7 (SD 4.01); n=43, Group 2: mean 2.05 (SD 2.86); n=43; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline scores (SD): homeopathic medicine 16.7 (3.7); placebo 16.5 (3.0).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason:

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Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - reduced activity at 7 months; Group 1: mean 2.72 (SD 4.47); n=43, Group 2: mean 1.81 (SD 2.82); n=43; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline scores (SD): homeopathic medicine 16.1 (3.1); placebo 16.4 (3.8).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Multidimensional fatigue inventory - reduced motivation at 7 months; Group 1: mean 1.35 (SD 4.15); n=43, Group 2: mean 1.65 (SD 3.02); n=43; Multidimensional fatigue inventory 4-20 Top=High is poor outcome; Comments: Baseline scores (SD): homeopathic medicine 13.0 (3.9); placebo 13.2 (3.7).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Fatigue impact scale - cognitive dimension at 7 months; Group 1: mean 4.88 (SD 9.3); n=43, Group 2: mean 4.21 (SD 7.18); n=43; Fatigue impact scale 0-40 Top=High is poor outcome; Comments: It is unclear if these are mean percentage changes or absolute changes in score. ANCOVA analysis with baseline outcome value as covariate.
Baseline scores (SD): homeopathic medicine 24.1 (9.0); placebo 24.2 (8.0).

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Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Fatigue impact scale - physical dimension at 7 months; Group 1: mean 4.98 (SD 8.5); n=43, Group 2: mean 5.3 (SD 6.69); n=43; Fatigue impact scale 0-40 Top=High is poor outcome; Comments: It is unclear if these are mean percentage changes or absolute changes in score. ANCOVA analysis with baseline outcome value as covariate.
Baseline scores (SD): homeopathic medicine 27.3 (6.8); placebo 27.4 (7.1).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire

- Actual outcome for adults; severity mixed or unclear: Fatigue impact scale - social dimension at 7 months; Group 1: mean 7.92 (SD 18.02); n=43, Group 2: mean 8.2 (SD 14.06); n=43; Fatigue impact scale 0-80 Top=High is poor outcome; Comments: It is unclear if these are mean percentage changes or absolute changes in score. ANCOVA analysis with baseline outcome value as covariate.
Baseline scores (SD): homeopathic medicine 44.8 (15.5); placebo 44.7 (16.4).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - Intention to treat analysis performed on actual data and imputed missing item data from those who returned partially completed questionnaires (all unit missing data excluded from analysis). The amount of missing data that has been imputed is not reported. Numbers below reflect excluded all unit missing data, not imputed missing data; Indirectness of outcome: No indirectness,

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Comments: NA; Baseline details: Baseline scores are comparable between groups. Age, gender, and duration of symptoms are comparable between groups; Blinding details: Trial coordinator requested a homeopathic pharmacy to dispense the prescribed remedy directly to the patient. Homeopathic medicines and placebos were identical in appearance and taste, and identically labelled. There was no direct contact between homeopaths/patients and homeopathic pharmacy; Group 1 Number missing: 10, Reason: Lost to follow-up/did not return final questionnaire; Group 2 Number missing: 7, Reason: Lost to follow-up/did not return final questionnaire	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Wiborg 2015[856]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=204)
Countries and setting	Conducted in Netherlands; Setting: outpatient clinic
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Department of Internal Medicine assessed the medical examination status of all patients and decided whether patients had been sufficiently examined by a medical doctor to rule out relevant medical explanations. If patients had not been sufficiently examined, they were seen for standard medical tests prior to referral to the outpatient clinic. In accordance with CDC recommendations, sufficient medical examination included evaluation of somatic parameters that may provide evidence for a plausible somatic explanation for prolonged fatigue. When abnormalities were detected in these tests, additional tests were made based on the judgement of the clinician of the Department of Internal Medicine who ultimately decided about the appropriateness of referral. Trained therapists ruled out psychiatric comorbidity as potential explanation for the complaints in unstructured clinical interviews.
Stratum	adults; severity mixed or unclear: at least 18 years of age; meeting CDC criteria - severe fatigue defined as a score of 35 or higher on the fatigue severity subscale of the Checklist Individual Strength and substantial impairment as a weighted total score of 700 or higher on the Sickness Impact Profile
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	At least 18 years of age; able to speak and read Dutch; meeting CDC criteria
Exclusion criteria	Patients who were in dispute over a disability pension were temporarily excluded from the trial

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Recruitment/selection of patients	Patients referred to the outpatient clinic for the management of chronic fatigue during the recruitment period and meeting eligibility criteria
Age, gender and ethnicity	Age - Mean (SD): CBT 38.1 (11.5), waiting list 37.3 (10.8) years. Gender (M:F): 47/157. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=136) Intervention 1: Psychological and behavioural interventions - CBT. 14 group sessions of 2 h within a period of 6 months. Included personal goal setting, fixing sleep-wake cycles, reducing the focus on bodily symptoms, a systematic challenge of fatigue-related beliefs, regulation and gradual increase in activities, and accomplishment of personal goals. Patients received a workbook with the content of the therapy. During sessions, patients were explicitly invited to give feedback about fatigue-related cognitions and behaviours to fellow patients. Group therapists (n=12) held degrees in psychology with the exception of a therapist who held a degree in pedagogy and a social worker with experience in group therapy, who also coordinated the group programme. All therapists were trained in manualised CBT for individual CFS patients. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: CBT was based on CBT used in earlier studies such as Bazelmans et al. 2005 which describes that CBT intervention as a course in 'coping with fatigue', targeting cognitions and behaviour known to perpetuate fatigue in CFS. Therapists were trained in CBT for CFS. Comments: 2 trial arms combined: CBT in groups of 8 patients and 2 therapists and CBT in groups of 4 patients and 1 therapist (n=68) Intervention 2: no treatment. Waiting list. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Funding not stated

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT versus NO TREATMENT

Protocol outcome 1: General symptom scales longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile at 6 months; Group 1: mean 800 (SD 664); n=136, Group 2: mean 1389 (SD 561); n=68; Sickness Impact Profile 0-5799 Top=High is poor outcome; Comments: Baseline values: CBT 1554 (533), waiting list 1495 (453)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 26, Reason: loss to follow up; Group 2 Number missing: 8, Reason: loss to follow up

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual Strength - fatigue severity sub scale at 6 months; Group 1: mean 33.5 (SD 13.6); n=136, Group 2: mean 46.6 (SD 8.5); n=68; Checklist Individual Strength - fatigue severity sub scale 8-56 Top=High is poor outcome; Comments: Baseline values: 50.9 (4.7), waiting list 49.9 (4.8)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 26, Reason: loss to follow up; Group 2 Number missing: 8, Reason: loss to follow up

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 - physical functioning at 6 months; Group 1: mean 74.4 (SD 22); n=136, Group 2: mean 63.3 (SD 21.1); n=68; SF36 physical functioning 0-100 Top=High is good outcome; Comments: Baseline values: CBT 55.4 (18.8), waiting list 60 (20)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 26, Reason: loss to follow up; Group 2 Number missing: 8, Reason: loss to follow up

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Symptom Checklist 90 - psychological distress at 6 months; Group 1: mean 135 (SD 32); n=136, Group 2: mean 153 (SD 38.5); n=68; Symptom Checklist 90 - psychological distress not reported Top=High is poor outcome; Comments: Baseline values: CBT 166 (37.3), waiting list 159 (38.3)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 26, Reason: loss to follow up; Group 2 Number missing: 8, Reason: loss to follow up

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Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Windthorst 2017[866]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Germany; Setting: outpatients
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 5 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: screened according to the CDC criteria; two structured clinical interviews for: DSM-IV Axis Disorders (SCID-I), the somatoform Disorder Schedule (SDS)
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants were screened according to the criteria for CFS of the CDC
Exclusion criteria	exclusion criteria included somatic or medical conditions that explained fatigue (e.g. cancer), substance abuse, a primary psychiatric disorder (e.g. schizophrenia), major depression or anxiety disorder, an ongoing psychotherapy or activation programme, and a body-mass index lower than 18.5 kg/m² or higher than 35 kg/m²; men were also excluded based on the knowledge that more women than men who experience CFS seek treatment
Recruitment/selection of patients	patients were recruited through advertisements in local newspapers and by an Internet web page
Age, gender and ethnicity	Age - Mean (SD): 50.7 (9.3). Gender (M:F): 0/24. Ethnicity: German
Further population details	-

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Extra comments	All female participants.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=13) Intervention 1: Exercise interventions - physical rehabilitation. Treatment consisted of 8 individual training sessions of 50 min each at weekly intervals and was carried out by a trained clinical psychologist. The aim of the first session was to become familiar with the setting, the equipment and the therapist. Each subsequent session started with a 10-min review of the diary, followed by a 20-30 min HRV-BF practice. The HRV-BF training included practicing slow inspiration and expiration with 6-10 breaths per minute, visualised on a monitor as two separate lines (breathing curve, heart rate) and meant to alter the individual stress reaction and to induce individual alleviation of tension. Period of exploring the body's reactions to the breathing and discussing these experiences alternated. After the practice interval, the therapist and patient reviewed the session records showing breathing, heart rate, skin conductance response and skin temperature. Interactions of physiology and emotion/cognition were discussed. By gaining experience with HRV-BF, patients were successively instructed to improve their RSA under real-life conditions such as imagining actual situations of stress. In addition to self-monitoring (diary keeping), homework was given in the form of daily practice exercises without the biofeedback device two times per day 5-10 min each time. Duration 8 weeks. Concurrent medication/care: Patients had to keep a diary in order to assess the intensity of their fatigue, their daily activities and their individual training at home and to connect these domains by exploring thoughts and feelings within the therapeutic contact. Keeping a diary too about 15 minutes per day. Homework was prescribed during the intervention; the diary and homework were discussed with patients at the beginning of each session. Indirectness: No indirectness Further details: 1. type of intervention: Not reported/unclear - carried out by a trained clinical psychologist Comments: comprised cognitive and behavioural strategies (n=15) Intervention 2: Exercise interventions - GET. Treatment consisted of 8 individual training sessions of 50 min each at weekly intervals and was carried out by a sports therapist and expert in sports medicine. The individual anaerobic threshold (IAS), collected by spirometry, was the individual training baseline. Patients were instructed in slow walking training on a treadmill adapted to their heart rate which equates about 70% of heart rate IAS. The duration and intensity were set at a level previously identified as achievable under spirometry testing and unlikely to exacerbate the patients' symptoms. The aim of the first session was to familiarise the patient with the setting, the equipment the treadmill and the therapist. The subsequent

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	sessions were subdivided to three parts comparable to the HRV-BF training. The sessions began with a review and discussion of the diary entries and the experience created by doing the exercises at home, followed by 20-30 min of waking training adapted to a moderate heart rate. At the end of the session, the sports therapist and patient reviewed the course of the session in regard to heart rate and physical reactions. Patients were encouraged to reduce resting and avoiding behaviour but simultaneously to watch carefully for symptoms and feelings of overload. In addition to continuing to keep a diary, homework consisted of two to three walking sessions per week at home (20-30 min), controlled by a pulse watch. Duration 8 weeks. Concurrent medication/care: Patients had to keep a diary in order to assess the intensity of their fatigue, their daily activities and their individual training at home and to connect these domains by exploring thoughts and feelings within the therapeutic contact. Keeping a diary too about 15 minutes per day. Homework was prescribed during the intervention; the diary and homework were discussed with patients at the beginning of each session. Indirectness: No indirectness Further details: 1. type of intervention: not reported/unclear - carried out by a sports therapist and expert in sports medicine
Funding	Other (Alfre-Teufel-Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GET versus HEART RATE VARIABILITY BIOFEEDBACK THERAPY (HRV-BF)

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 Mental summary-QoL at 5 months; Group 1: mean 38.3 (SD 15.3); n=11, Group 2: mean 51 (SD 8.9); n=13; SF-36- Mental functioning subscale 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Blinding details: Lack of participant blinding was due to the different nature of the interventions and is not likely to have influenced the results; this is judged as high risk of bias as details about the outcome assessors are not given; Group 1 Number missing: 4, Reason: drop-out due to lack of benefit from intervention; Group 2 Number missing: 2, Reason: did not complete questionnaire but their last values were carried forward

- Actual outcome for adults; severity mixed or unclear: SF36 Physical summary-QoL at 5 months; Group 1: mean 46.6 (SD 7.1); n=15, Group 2: mean 47.1 (SD 12.2); n=13; SF-36- physical function subscale 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Potential difference in baseline scores, GET: 37.7(7.8) vs HRV-BF: 42.6 (9.2); Blinding details: Lack of participant blinding was due to the different nature of the interventions and is not likely to have

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influenced the results; this is judged as high risk of bias as details about the outcome assessors are not given; Group 1 Number missing: 4, Reason: drop-out due to lack of benefit from intervention; Group 2 Number missing: 2, Reason: did not complete questionnaire but their last values were carried forward Protocol outcome 2: Fatigue at longest follow up available - Actual outcome for adults; severity mixed or unclear: Total fatigue (MFI-total) at 5 months; Group 1: mean 55.6 (SD 21.3); n=11, Group 2: mean 43.6 (SD 15.9); n=13 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Baseline details: Difference in baseline scores may have influence results: GET: 68.8(10.1) vs HRV-BF: 61.5 (9.7); Blinding details: Lack of participant blinding was due to the different nature of the interventions and is not likely to have influenced the results; this is judged as high risk of bias as details about the outcome assessors are not given; Group 1 Number missing: 4, Reason: drop-out due to lack of benefit from intervention; Group 2 Number missing: 2, Reason: did not complete questionnaire but their last values were carried forward Protocol outcome 3: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Depression – patient health questionnaire at 5 months; Group 1: mean 8.8 (SD 6); n=11, Group 2: mean 4.2 (SD 3.1); n=13; PHQ-9 (Patient health questionnaire) 0-27 Top=High is poor outcome; Comments: 9 items (mood, sleep, fatigue, appetite, self-confidence, concentration, interest in doing things, psychomotorics and suicidal tendency); scores 5 to 10 represent cut-off points for minor and major depressive symptoms Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness; Blinding details: Lack of participant blinding was due to the different nature of the interventions and is not likely to have influenced the results; this is judged as high risk of bias as details about the outcome assessors are not given; Group 1 Number missing: 4, Reason: drop-out due to lack of benefit from intervention; Group 2 Number missing: 2, Reason: did not complete questionnaire but their last values were carried forward	
Protocol outcomes not reported by the study	Mortality at longest follow up available; General symptom scales longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Physical functioning at longest follow-up available

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Study	Witham 2015[868]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in United Kingdom; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients required to have diagnosed CFS which fulfilled 1994 Fukuda criteria and Canadian criteria
Stratum	adults; severity mixed or unclear: Adults (≥18 years); no info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Age ≥18 years; diagnosed CFS which fulfilled 1994 Fukuda criteria and Canadian criteria; serum 25OHD level <75nmol/L
Exclusion criteria	History of osteoporosis, sarcoidosis, renal stones, metastatic malignancy; already taking pharmacological vitamin D preparations (fish oils permitted); liver function tests (bilirubin, alanine, aminotransferase or alanine phosphatase) >3x ULN, corrected calcium >2.6mmol/L or <2.15mmol/L;=, eGFR <40ml/min; unable to give written consent; childbearing age and not taking reliable contraception; pregnant; diagnosed with psychiatric disorders within last 5 years; substance abuse/dependence or eating disorder diagnosed at any time.
Recruitment/selection of patients	Participants recruited from a connective tissue disease clinic via advertising in local ME patient support groups and ME research organisation magazine

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Age, gender and ethnicity	Age - Mean (SD): Vit D 48.1 (12); placebo 50.7 (13.1). Gender (M:F): 12/38. Ethnicity: Not reported
Further population details	-
Extra comments	Mean (SD), Vit D/placebo: BMI 28.8 (7.9)/29.8 (5.4); 25OHD nmol/L 44 (15)/48 (20) (12% of participants had levels <25nmol/L) A large number of other baseline measures were recorded (various blood tests, certain medical conditions and medication use; heart rate and blood pressure, vascular USS measurements).
Indirectness of population	Serious population indirectness: Study only included subset of CFS population who also had 25OHD (serum vit D) level <75nmol/L.
Interventions	(n=25) Intervention 1: dietary supplementation - Vit D. A single dose of 100,000 units of oral vit D3 (Vigantol oil), 20,000 units vit D3 per ml, administered at baseline, 2 months, and 4 months. Medication ingested in presence of study team. Duration 6 months. Concurrent medication/care: Statin use n=2; antiplatelet use n=0; antihypertensive use n=4; median number of medications (IQR) 2 (4). Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable (n=25) Intervention 2: placebo or sham - placebo/sham. A single dose of placebo (Mygliol oil), administered at baseline, 2 months, and 4 months. Medication ingested in presence of study team. Duration 6 months. Concurrent medication/care: Statin use n=4; antiplatelet use n=3; antihypertensive use n=5; median number of medications (IQR) 4 (4). Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not applicable
Funding	Other (Study funded by charitable organisation (ME Research UK) and government (NHS Tayside); study drugs provided by industry (Merck KGaA))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VIT D versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Piper fatigue scale at 6 months; MD; 0.2 (95%CI -0.8 to 1.2) (p-value: 0.73) Piper fatigue scale 0-10

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Top=High is poor outcome, Comments: Baseline/follow-up scores, mean (SD): vit D, n=21 6.3, (1.9)/6.6 (1.1); placebo, n=24, 7.3 (1.2)/7.0 (1.9).
MD, reported as 'treatment effect' adjusted for baseline values;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome - Study reports ITT analysis but does not define this further, so number analysed unclear; no mention of imputation. Reasons/numbers below are taken from consort diagram. High risk assigned due to potentially significant differential reasons for patient drop-outs between groups.
Outcome reporting - all outcomes measured at baseline, 2 months, 4 months, and 6 months. Only one time point reported for this outcome and unclear which time point is reported; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, BMI, 25OHD levels. A large number of other baseline details were reported but unlikely to all be relevant for this outcome. Baseline outcome measure is not reported but outcome adjusted for this. ; Blinding details: Matching placebo; Group 1 Number missing: 4, Reason: Too unwell to attend follow-up visit; Group 2 Number missing: 1, Reason: Unable to attend follow-up visit within time-frame

Protocol outcome 2: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Adverse events - deaths at 6 months; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome - Study reports ITT analysis but does not define this further, so number analysed unclear. Assumed all patients included for this outcome so low risk assigned. ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, BMI, 25OHD levels, past history of cancer, vascular disease, diabetes mellitus. Placebo group tended to be on a higher number of medications. A large number of other baseline details were reported but unlikely to all be relevant for this outcome. ; Blinding details: Matching placebo; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - depression subscale at 6 months; MD; -1.0 (95%CI -2.6 to 0.5) (p-value: 0.18) Hospital anxiety and depression scale 0-21 Top=High is poor outcome, Comments: Baseline/follow-up scores, mean (SD): vit D, n=21, NR/5.7 (3.1); placebo, n=24, NR/7.6 (4.6). MD, reported as 'treatment effect' adjusted for baseline values;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome - Study reports ITT analysis but does not define this further, so number analysed unclear; no mention of imputation. Reasons/numbers below are taken from consort diagram. High risk assigned due to potentially significant differential reasons for patient drop-outs between groups.
Outcome reporting - all outcomes measured at baseline, 2 months, 4 months, and 6 months. Only one time point reported for this outcome and unclear which time point is reported; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, BMI, 25OHD levels. A large number of other baseline details were reported but unlikely to all be relevant for this outcome. Baseline outcome measure is not reported but

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outcome adjusted for this; Blinding details: Matching placebo; Group 1 Number missing: 4, Reason: Too unwell to attend follow-up visit; Group 2 Number missing: 1, Reason: Unable to attend follow-up visit within time-frame - Actual outcome for adults; severity mixed or unclear: Hospital anxiety and depression scale - anxiety subscale at 6 months; MD; 0.4 (95%CI -0.9 to 1.8) (p-value: 0.53) 0-21 Hospital anxiety and depression scale Top=High is poor outcome, Comments: Baseline/follow-up scores, mean (SD): vit D, n=21, NR/5.7 (4.0); placebo, n=24, NR/5.0 (4.4). MD, reported as 'treatment effect' adjusted for baseline values; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Incomplete outcome - Study reports ITT analysis but does not define this further, so number analysed unclear; no mention of imputation. Reasons/numbers below are taken from consort diagram. High risk assigned due to potentially significant differential reasons for patient drop-outs between groups. Outcome reporting - all outcomes measured at baseline, 2 months, 4 months, and 6 months. Only one time point reported for this outcome and unclear which time point is reported; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, BMI, 25OHD levels. A large number of other baseline details were reported but unlikely to all be relevant for this outcome. Baseline outcome measure is not reported but outcome adjusted for this. ; Blinding details: Matching placebo; Group 1 Number missing: 4, Reason: Too unwell to attend follow-up visit; Group 2 Number missing: 1, Reason: Unable to attend follow-up visit within time-frame	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Study	Wright 2005[874]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=13)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year (+ additional 6 months follow-up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All participants were assessed by a paediatrician prior to entry into the study, Oxford criteria for diagnosis used (with modification for children of 3 months fatigue).
Stratum	Children and young people, severe: Age range 8.9-16.9 years (age group breakdown: 0-11: n=1; 12-14: n=7; 15-19: n=5); in mainstream schools; incapacitated by CFS to the point of not being able to attend school; markedly restricted in their ability to walk from the house, but not permanently bed or wheelchair bound.
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Young people with CFS meeting the Oxford criteria (with modification for children of 3 months fatigue); gave informed consent
Exclusion criteria	Other fatiguing medical conditions; pre-existing ongoing treatment for CFS
Recruitment/selection of patients	Potential participants with either known CFS or more than 2 weeks off school because of physical symptoms but no clear diagnoses were identified by local professionals from health/social/education services over a 15 month period
Age, gender and ethnicity	Age - Range: 8.9-16.9 years. Gender (M:F): 5/8. Ethnicity: Not reported

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Further population details	-
Extra comments	Duration of illness (median): pacing group 14.5 months; stairway group 12.0 months (all were newly diagnosed) - breakdown of duration of illness: <1 year n=6, 1-2 years n=5, >2 years n=2. Age group breakdown (years): 0-11: pacing group n=0, stairway group n=1; 12-14: pacing group n=4, stairway group n=3; 15-19: pacing group n=2, stairway group n=3.
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature.
Interventions	(n=6) Intervention 1: self-management - pacing. Clinic appointments weekly for 1 month, 2 weekly for the next 3 months, 3 weekly for 2 months, and 4 weekly for 6 months. Three clinicians conducted the treatment sessions using treatment manuals. Pacing activity to the changing needs and responses of the body by exercising to the point of tolerance, avoiding overexertion; managing energy within an overall limit ("glass ceiling"); resting when necessary, but avoiding total rest; avoiding physically and/or emotionally stressful situations until ready; tailoring return to school to the needs of the young person, taking careful heed of symptoms, the child, and the family. Both treatment arms included a strong emphasis on collaboration with patient and family; support and advice to establish a healthy diet, and health sleep patterns; cooperative work between child mental health professionals and paediatricians. Collaboratively agreed targets were set around nutrition, activity, sleep, social activity, emotional factors and school reintegration. Participants monitored these using a diary. Participants were not expected to do any activities they had not agreed. Participants were encouraged to discuss constructively how their lifestyles, temperaments and approaches to life may impact on illness or recovery. A tailored gradual return to school and social activity was planned where possible. Duration 1 year. Concurrent medication/care: All participants were seen by the paediatrician every 12 weeks. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (3 clinicians delivered the intervention using treatment manuals). (n=7) Intervention 2: Psychological and behavioural interventions - pragmatic rehabilitation. Clinic appointments weekly for 1 month, 2 weekly for the next 3 months, 3 weekly for 2 months, and 4 weekly for 6 months. Three clinicians conducted the treatment sessions using treatment manuals. The stairway to health programme involved a structured tailored incremental rehabilitation programme. Time was spent providing a holistic understanding of CFS that moved away from an exclusively physical or exclusively

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	psychological understanding of the illness; explaining vicious cycles that exacerbate illness, including those of nutrition, sleep patterns, physical deconditioning, social isolation, educational estrangement, and emotional cycles (including loss of self-esteem and confidence); bolstering adaptive coping strategies and re-evaluating negative attributions about the illness and the future. Both treatment arms included a strong emphasis on collaboration with patient and family; support and advice to establish a healthy diet, and health sleep patterns; cooperative work between child mental health professionals and paediatricians. Collaboratively agreed targets were set around nutrition, activity, sleep, social activity, emotional factors and school reintegration. Participants monitored these using a diary. Participants were not expected to do any activities they had not agreed. Participants were encouraged to discuss constructively how their lifestyles, temperaments and approaches to life may impact on illness or recovery. A tailored gradual return to school and social activity was planned where possible. Duration 1 year. Concurrent medication/care: All participants were seen by the paediatrician every 12 weeks. 1 participant received an antidepressant. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (3 clinicians delivered the intervention using treatment manuals.).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PACING versus STAIRWAY TO HEALTH PROGRAMME

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for children; severity mixed or unclear: Child health questionnaire - global health at 12 months; Group 1: mean 4.2 (SD 0.837); n=5, Group 2: mean 2.2 (SD 0.447); n=6; Child health questionnaire 1-5 Top=High is poor outcome; Comments: Baseline scores (SD): pacing group 4.2 (0.837); stairway group 4.0 (1.095). ANCOVA controlling for baseline scores reported as 'difference' with 95% CI (pacing subtracted from stairway), does not specify mean difference: -1.8 (-0.94, -2.74), p value 0.002
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, length of illness, baseline score; Blinding details: Subjective patient reported outcome. Researcher conducting assessment interviews was blind to treatment allocation. 1 participant in stairway arm received an antidepressant; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 2: General symptom scales longest follow up available

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- Actual outcome for children; severity mixed or unclear: Young person functional ability scale at 12 months; Group 1: mean 68.5 percentage (SD 27.02); n=5, Group 2: mean 81.25 percentage (SD 17.59); n=6; Young person functional ability scale (AYME) 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 67.00 (18.23); stairway group 52.50 (22.75). ANCOVA controlling for baseline scores reported as 'difference' with 95% CI (pacing subtracted from stairway), does not specify mean difference: 17.0 (-17.0, 51.0), p value 0.28
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, length of illness. Baseline score difference of 14.5 points; Blinding details: Subjective patient reported outcome. Researcher conducting assessment interviews was blind to treatment allocation. 1 participant in stairway arm received an antidepressant; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 3: Fatigue at longest follow up available
- Actual outcome for children; severity mixed or unclear: Chalder's fatigue scale (14-item) at 12 months; Group 1: mean 18 (SD 6.519); n=5, Group 2: mean 14 (SD 9.582); n=6; Chalder's fatigue scale 0-42 Top=High is poor outcome; Comments: Baseline scores (SD): pacing group 23.2 (9.23); stairway group 32.17 (6.113). ANCOVA controlling for baseline scores reported as 'difference' with 95% CI (pacing subtracted from stairway), does not specify mean difference: -5.2 (-19.8, 9.49), p value 0.44
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, length of illness. Baseline score difference of 8.97 points; Blinding details: Subjective patient reported outcome. Researcher conducting assessment interviews was blind to treatment allocation. 1 participant in stairway arm received an antidepressant; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for children; severity mixed or unclear: Birleson depression rating scale at 12 months; Group 1: mean 12.6 (SD 6.58); n=5, Group 2: mean 10.67 (SD 4.844); n=6; Birleson depression scale 0-36 Top=High is poor outcome; Comments: Baseline scores (SD): pacing group 14.00 (5.657); stairway group 15.83 (5.529). ANCOVA controlling for baseline scores reported as 'difference' with 95% CI (pacing subtracted from stairway), does not specify mean difference: -2.99 (-10.0, 4.06), p value 0.36
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, length of illness, baseline score; Blinding details: Subjective patient reported outcome. Researcher conducting assessment interviews was blind to treatment allocation. 1 participant in stairway arm received an antidepressant; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported

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- Actual outcome for children; severity mixed or unclear: Hospital anxiety and depression scale - anxiety score at 12 months; Group 1: mean 6.6 (SD 4.73); n=5, Group 2: mean 6 (SD 3.63); n=6; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Baseline scores (SD): pacing group 6.8 (3.56); stairway group 10.17 (3.71). ANCOVA controlling for baseline scores reported as 'difference' with 95% CI (pacing subtracted from stairway), does not specify mean difference: -1.60 (-8.31, 5.10), p value 0.60 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, length of illness. Baseline score difference of 3.37 points; Blinding details: Subjective patient reported outcome. Researcher conducting assessment interviews was blind to treatment allocation. 1 participant in stairway arm received an antidepressant; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported Protocol outcome 5: Return to school or work at longest follow up available - Actual outcome for children; severity mixed or unclear: School attendance at 6 months after treatment concluded; Group 1: mean 28.7 percentage (SD 36.24); n=5, Group 2: mean 84.6 percentage (SD 34.8); n=6; School attendance (percentage of possible half days attended in a 6 month period) 0-100 Top=High is good outcome; Comments: Baseline scores (SD): pacing group 45.74 (29.92); stairway group 45.25 (40.90). ANCOVA controlling for baseline scores reported as 'difference' with 95% CI (pacing subtracted from stairway), does not specify mean difference: 56.1 (6.3, 105.7), p value 0.032 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender, length of illness, baseline score; Blinding details: Subjective patient reported outcome. Researcher conducting assessment interviews was blind to treatment allocation. 1 participant in stairway arm received an antidepressant; Group 1 Number missing: 1, Reason: Not reported; Group 2 Number missing: 1, Reason: Not reported	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Exercise performance measure at longest follow up available

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Study	Zhang 2015[886]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in China; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were hospitalized patients or outpatients of a CFS specialist outpatient unit meeting the CDC diagnostic criteria (Fukuda 1994); had undergone medical examination to exclude other causes of chronic fatigue.
Stratum	Severity and age mixed or unclear: Inclusion criteria age 15-60 (but average age suggests mostly adults); inpatients and outpatients - no further info on severity
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients meeting the diagnostic criteria of CFS (Fukuda 1994), and the TCM definition for liver stagnation and spleen deficiency syndrome; males or females age 15-60 years; CFS symptoms persisted or recurred for ≥6 consecutive months; had undergone state examination and routine physical examination, including blood and urine tests, to exclude other causes of chronic fatigue; loved music and would listen to music at least 5 hours per week; agreed to participate voluntarily and provided written informed consent
Exclusion criteria	Age <15 or >60; chronic fatigue explained by other primary causes; mental disorders including bipolar, schizophrenia, delusional disorder, dementia, anorexia nervosa; Hamilton Depression Scale score ≥17, indicating depression; Hamilton Anxiety Scale score ≥14, indicating anxiety disorder; hearing disorders meaning they could not hear the rhythm of the music; did not like music and did not have a habit of listening to music; pregnant women or those who had given birth <1 year prior; undergone surgery in past year;

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	obese patients with BMI >40; undergone other relevant treatments; mentally challenged patients; allergic to recipe used in the study
Recruitment/selection of patients	Participants were hospitalized or outpatients of a CFS specialist outpatient unit
Age, gender and ethnicity	Age - Mean (SD): control group 41.2 (13.1) years; music groups combined 44.3 (12) years. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	-
Extra comments	Treatment groups mean ages/SDs combined, excluding treatment group 5 due to typo in paper (reported as age 4.1, SD 12)
Indirectness of population	Very serious indirectness: Only a subset of people with CFS who also met the traditional Chinese medicine definition for liver stagnation and spleen deficiency syndrome were included and 1994 CDC criteria used; PEM is not a compulsory feature.
Interventions	(n=75) Intervention 1: complementary therapies - music therapy. Participants were required to listen to music from the Five Element Music compact disc for 5 days a week, with a 2 day rest; 45 min sessions, starting at either 12pm or 7pm each day; volume of 55-65 dB in a quiet environment; tape recorders, intensity of music, patient's location kept constant throughout study; the importance of music therapy was emphasized in the first treatment. Participants were also given Lixujieyu recipe (Chinese medicine); recipe prepared by study hospital pharmacy department; 300ml designated as one dose, with half a dose administered in the morning and the other half administered in the evening. Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (Music (from CD) and traditional Chinese remedy prepared in hospital pharmacy. Participants were either hospitalized patients or outpatients of CFS specialist outpatient unit; professional clinicians instructed patients on how to fill in scales). Comments: There were 5 treatment groups (n=15 each) which differed only on subtype of music: Gong-Tune, Jiao-Tune, Yu-Tune, Shang-Tune, or Zhi-Tune. These groups have been combined for the purposes of this review. (n=15) Intervention 2: complementary therapies - traditional Chinese medicine. Participants were given

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	Lixujieyu recipe (Chinese medicine); recipe prepared by study hospital pharmacy department; 300ml designated as one dose, with half a dose administered in the morning and the other half administered in the evening. Duration 4 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. type of intervention: Not stated / Unclear (Traditional Chinese remedy prepared in hospital pharmacy. Participants were either hospitalized patients or outpatients of CFS specialist outpatient unit; professional clinicians instructed patients on how to fill in scales).
Funding	Academic or government funding (General Program of the National Natural Science Foundation; State Administration of Traditional Chinese Medicine)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIVE ELEMENTS MUSIC THERAPY + LIXUJIEYU RECIPE versus LIXUJIEYU RECIPE ALONE

Protocol outcome 1: Fatigue at longest follow up available

- Actual outcome for Severity and age mixed or unclear: Fatigue scale (based on Chalder fatigue scale) at 4 weeks; Group 1: mean 17.54 (SD 5.281); n=75, Group 2: mean 20.2 (SD 4); n=15; Fatigue scale unclear Top=High is poor outcome; Comments: Baseline scores, mean (SD): music 20.52 (4.039); lixujieyu 22.6 (2.8)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Measurement bias - scale reported as 'based on Chalder fatigue scale', but no further details to clarify how/if the scale differed from Chalder fatigue scale. Range not reported; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, duration of illness, and baseline scores; Blinding details: Subjective patient-rated scores; Group 1 Number missing: , Reason: NA; Group 2 Number missing: , Reason: NA

Protocol outcome 2: Psychological status at longest follow up available

- Actual outcome for Severity and age mixed or unclear: Hamilton depression scale at 4 weeks; Group 1: mean 10.4 (SD 3.2); n=75, Group 2: mean 11.5 (SD 3.2); n=15; Hamilton depression scale 0-52 Top=High is poor outcome; Comments: Baseline scores (SD): music + lixujieyu group 12.6 (2.8); lixujieyu group 11.7 (3.2)

Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, duration of illness, and baseline scores; Blinding details: Subjective patient-rated scores; Group 1 Number missing: , Reason: NA; Group 2 Number missing: , Reason: NA

- Actual outcome for Severity and age mixed or unclear: Hamilton anxiety scale at 4 weeks; Group 1: mean 9.4 (SD 2.1); n=75, Group 2: mean 10.5 (SD

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1.8); n=15; Hamilton anxiety scale 0-56 Top=High is poor outcome; Comments: Baseline scores (SD): music + lixujieyu group 11.3 (1.6); lixujieyu group 11.4 (1.3) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments -; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, duration of illness, and baseline scores; Blinding details: Subjective patient-rated scores; Group 1 Number missing: , Reason: NA; Group 2 Number missing: , Reason: NA	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; General symptom scales longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available

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Appendix E Forest plots

E.1 Self-management

E.1.1 Self-management versus Relaxation: adults, severity mixed or unclear

Figure 2: Quality of life (SF36 sub scales)

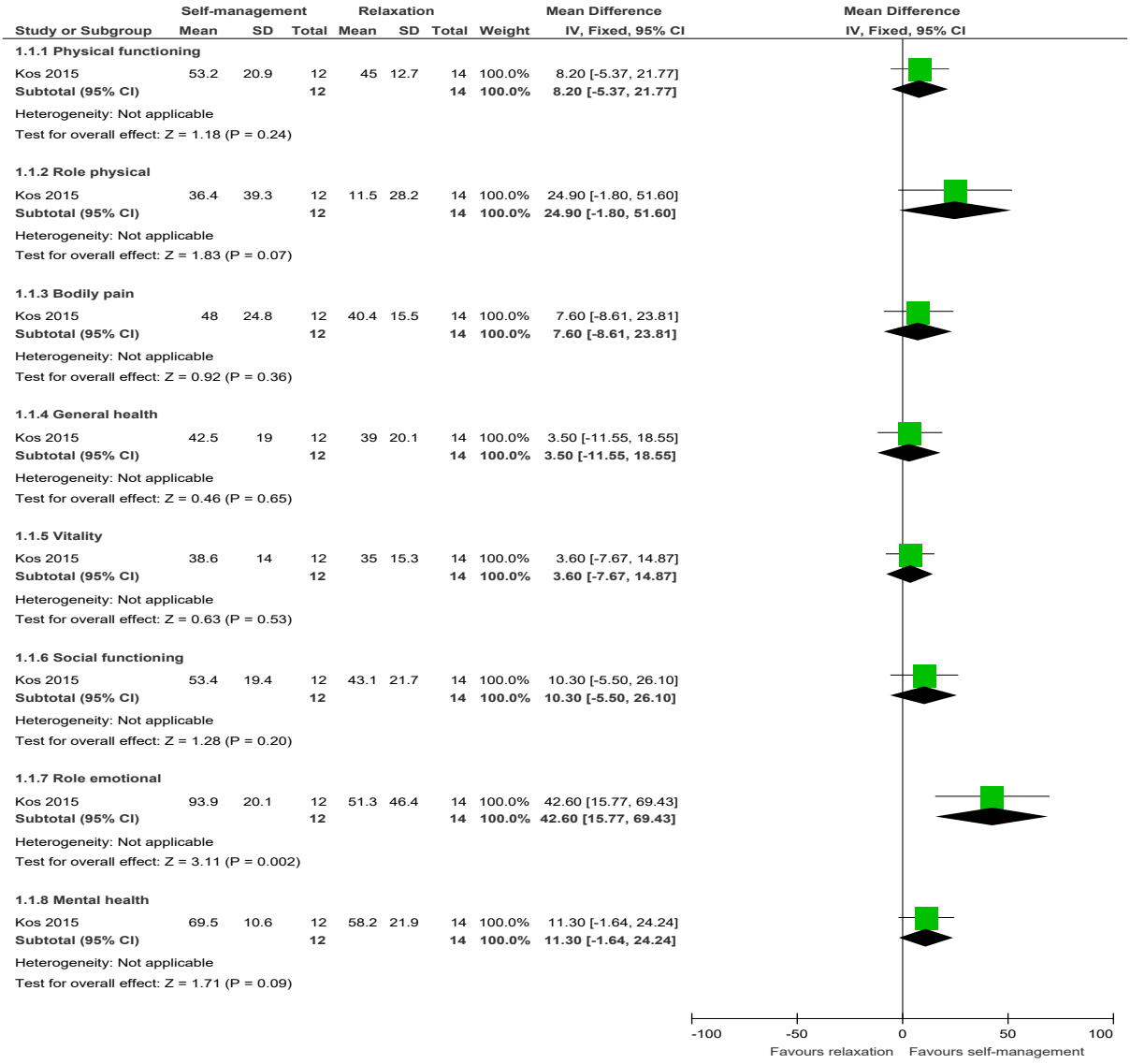

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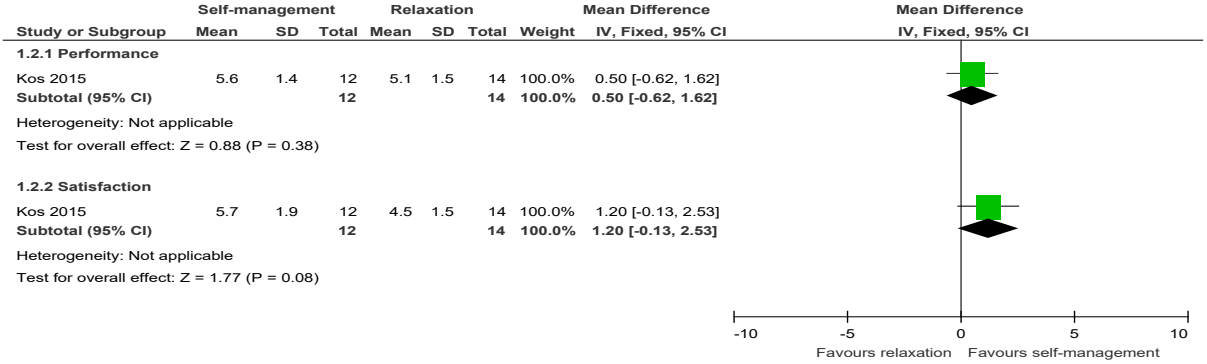
Figure 3: Physical function (Canadian Occupational Performance Measure)



E.1.2 Self-management (programme) versus Usual care: adults, severity mixed or unclear

Figure 4: Quality of life (SF36)

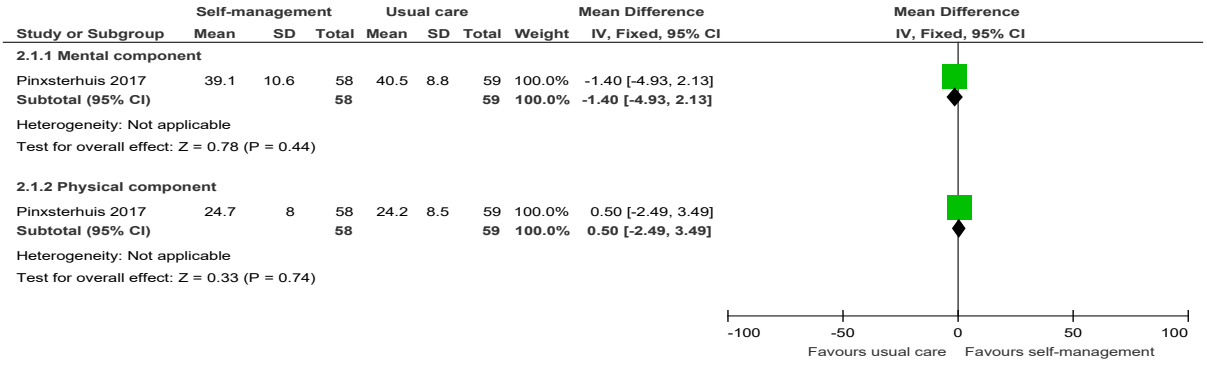
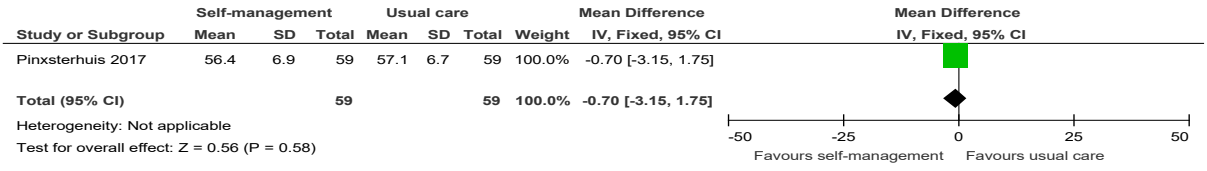


Figure 5: Fatigue (Fatigue Severity Scale)



E.1.3 Self-management (adaptive pacing therapy) versus usual care: adults, severity mixed or unclear

Figure 6: Quality of life (EQ5D)

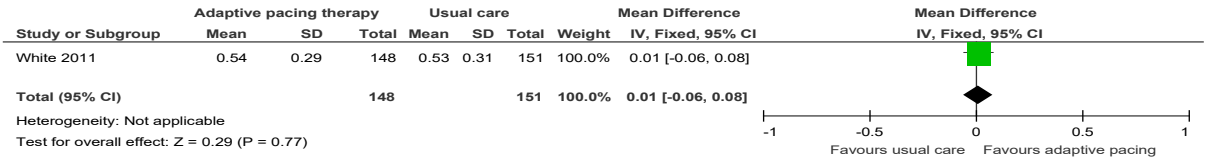


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Figure 7: General symptom scales (proportion with positive change (very much better or much better))

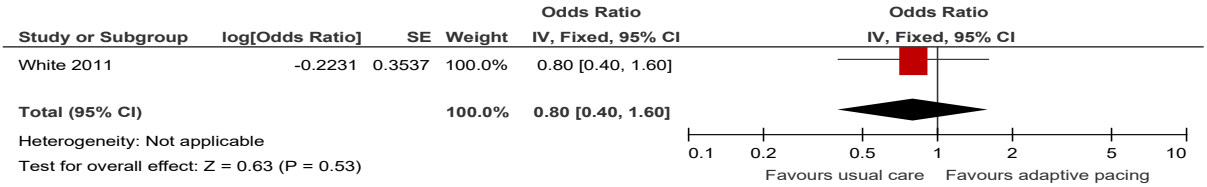

Figure 8: Fatigue/fatigability (Chalder fatigue scale)

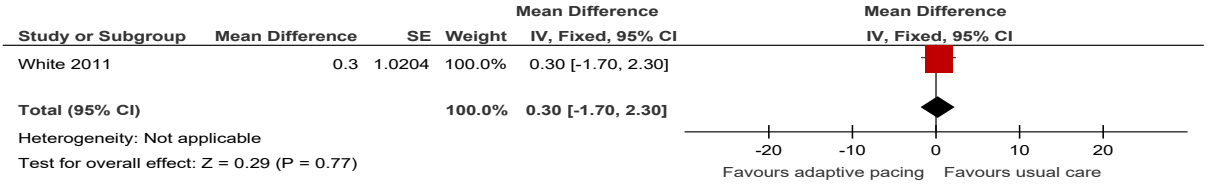

Figure 9: Physical function (SF36 physical function)

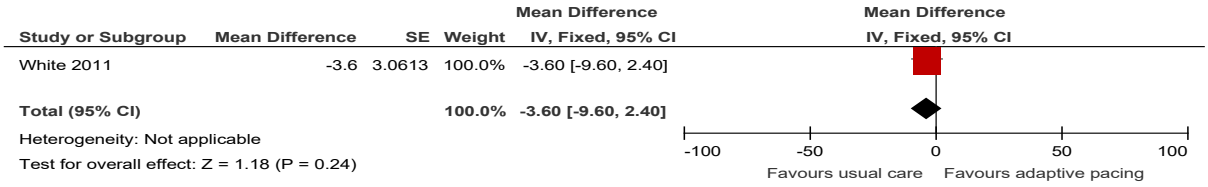

Figure 10: Psychological status (HADS anxiety)

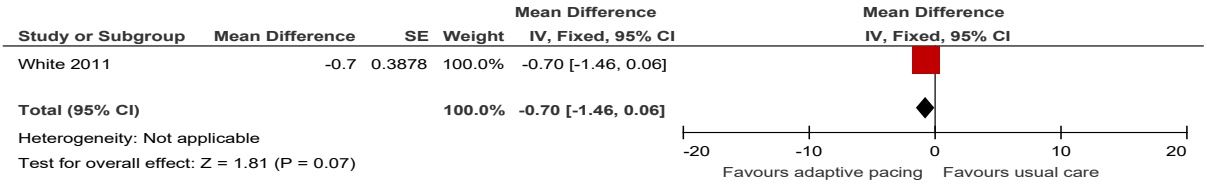

Figure 11: Psychological status (HADS depression)

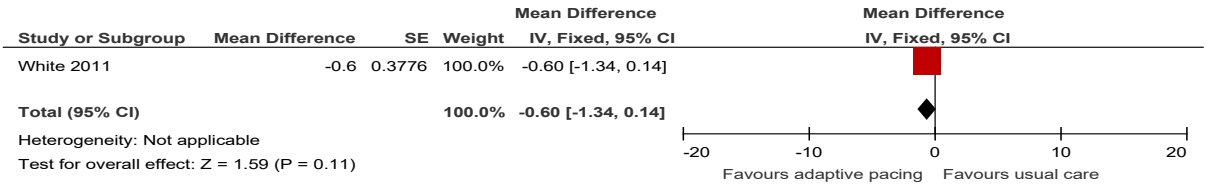

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Figure 12: Pain (numeric rating scale)

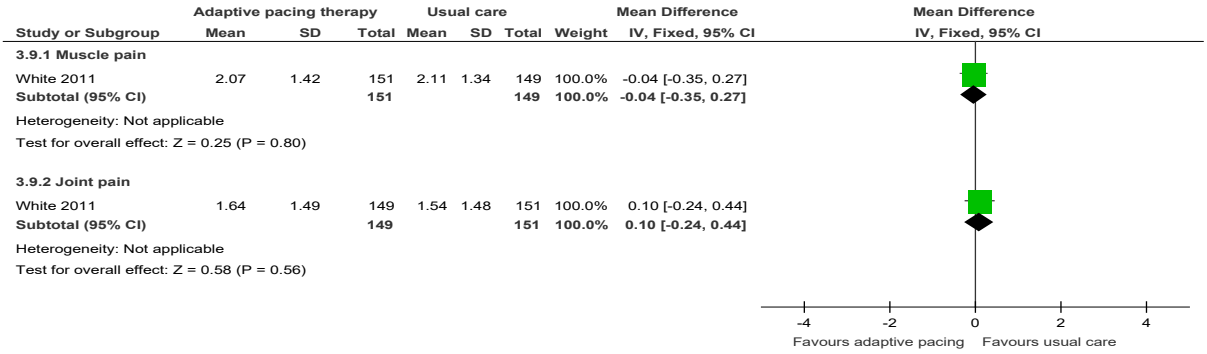

Figure 13: Sleep quality (Jenkins sleep scale)

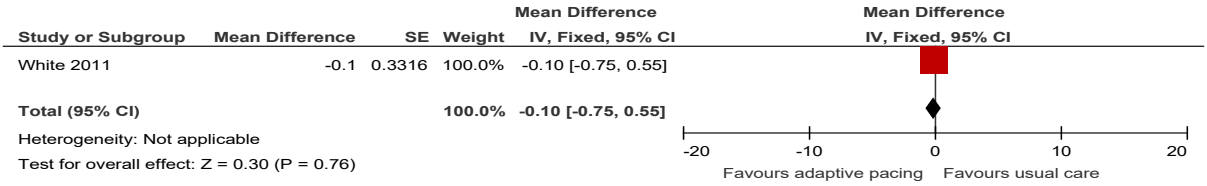

Figure 14: Return to school/work (Work and social adjustment scale)

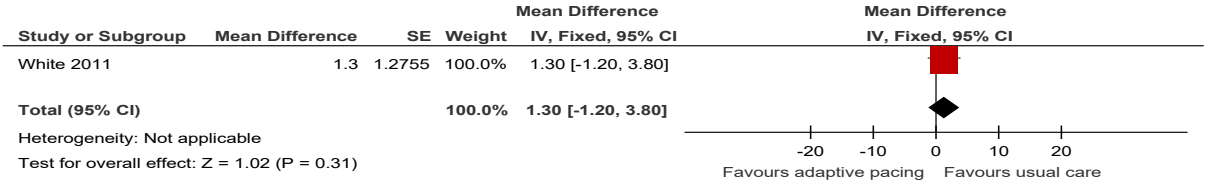

Figure 15: Adverse events (non-serious)

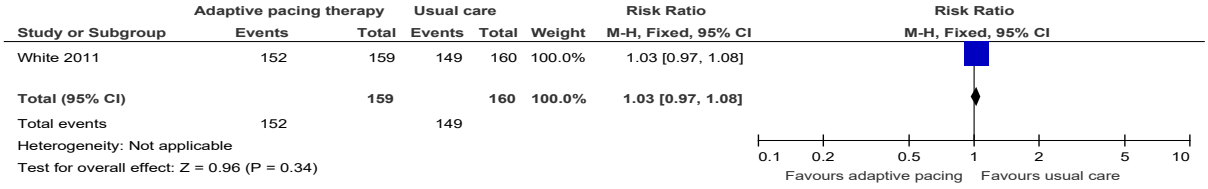

Figure 16: Adverse events (serious)

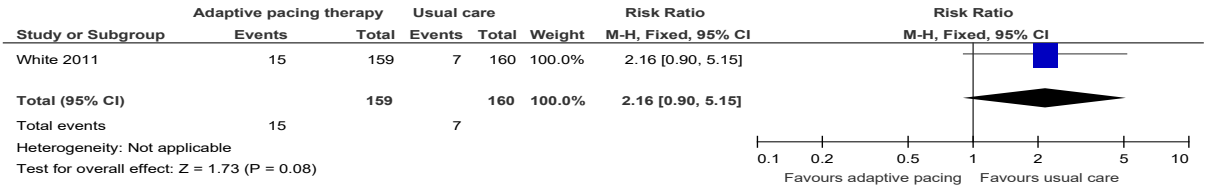

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Figure 17: Adverse events (adverse reactions)

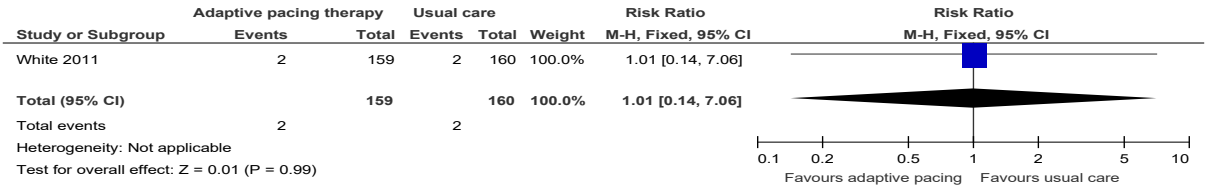
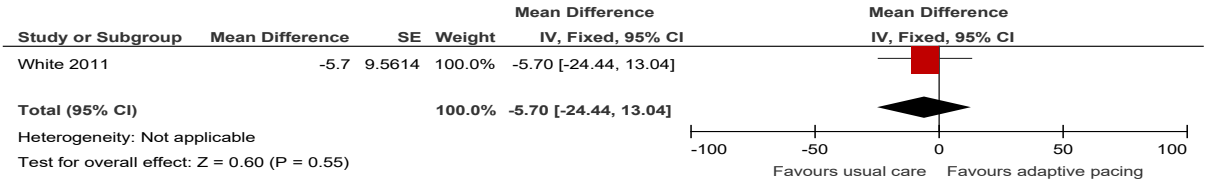


Figure 18: Exercise performance measure (6 minute walk test)



E.1.4 Self-management versus Usual care: adults; severe

Figure 19: Fatigue (Fatigue severity scale)

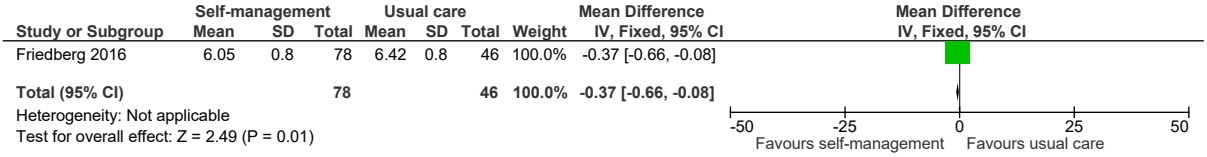


Figure 20: Physical functioning (SF36 physical function)

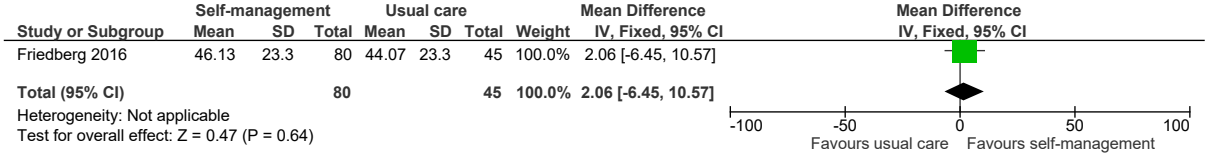


Figure 21: Psychological status (Beck depression inventory)

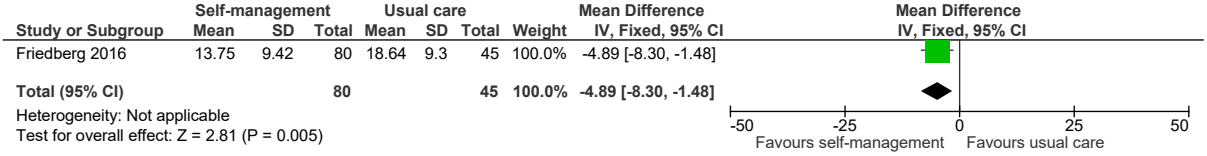


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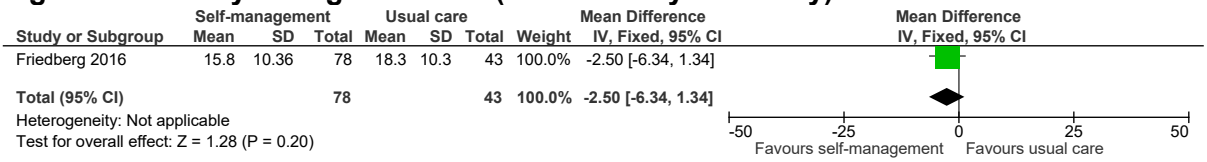
Figure 22: Psychological status (Beck anxiety inventory)



E.1.5 Self-management versus Stairway to health programme: children and young people; severe

Figure 23: Quality of life (Child Health Questionnaire)

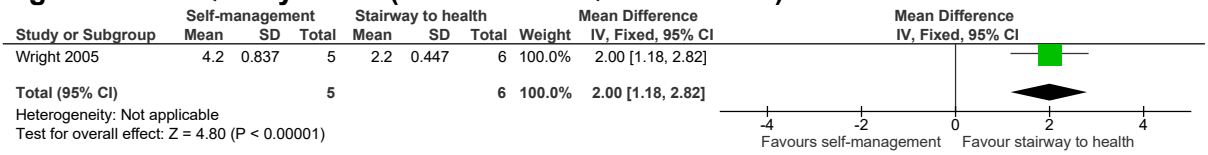


Figure 24: General symptom scales (Young Person Functional Ability Scale)

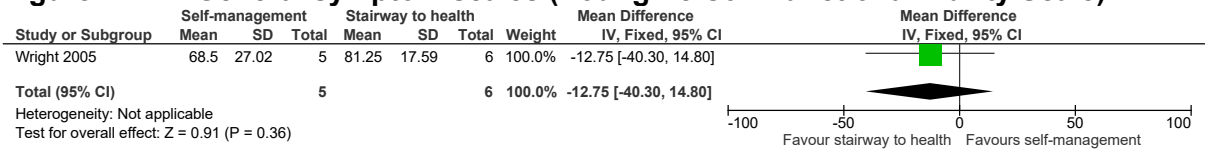


Figure 25: Fatigue (Chalder Fatigue Scale)

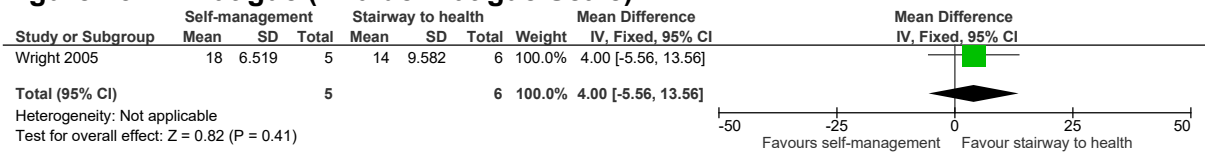


Figure 26: Psychological status (Birleson Depression Scale)

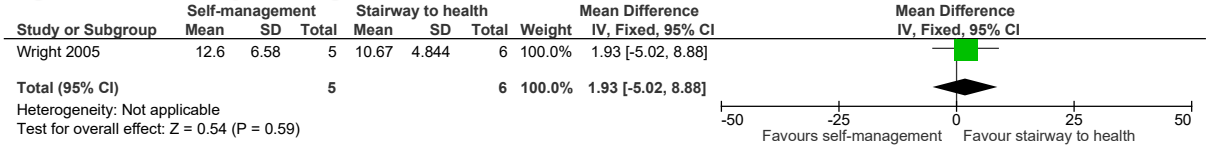


Figure 27: Psychological status (Hospital Anxiety and Depression Scale – anxiety)

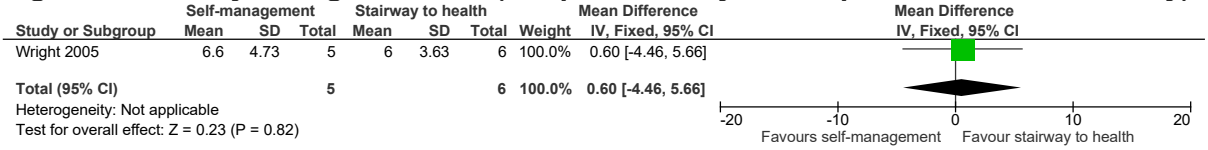


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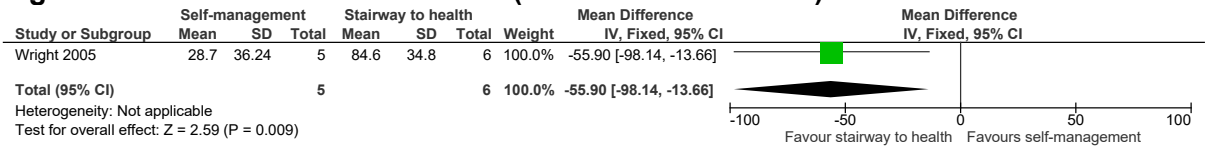
Figure 28: Return to school/work (% school attendance)



E.2 Psychological/behavioural interventions

Cognitive behavioural therapy

E.2.1 Cognitive behavioural therapy versus usual care: adults, severity mixed or unclear

Figure 29: Quality of life (EQ5D) - individual face-to-face CBT

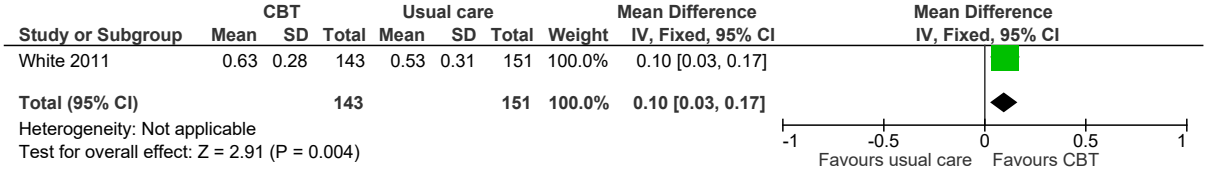


Figure 30: Quality of life (SF36) – group-based CBT

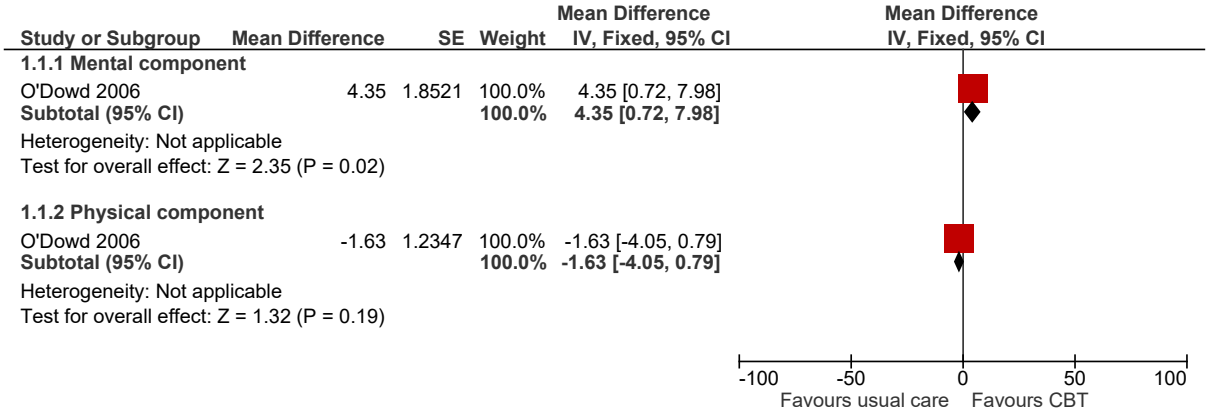


Figure 31: Quality of life (Health status (HUI3)) – group-based CBT

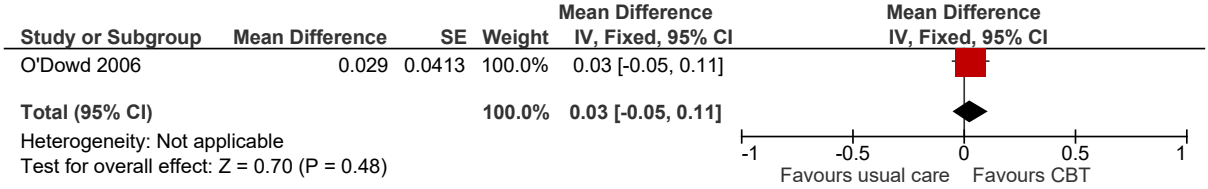


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Figure 32: General symptom scales (Clinical Global Impression scale - positive change (very much better or much better)) – individual face-to-face CBT

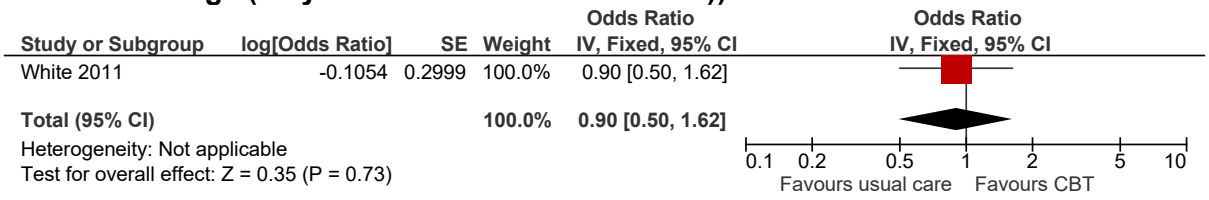

Figure 33: General symptom scales (Sickness Impact profile 8) – web/written CBT

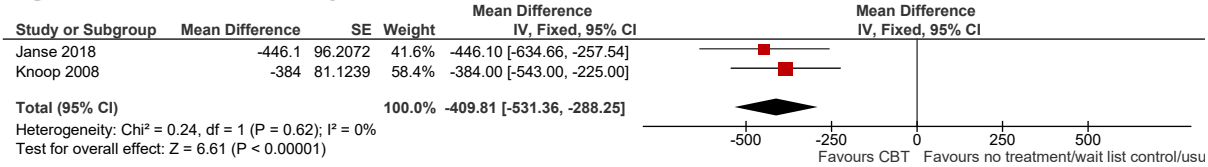

Figure 34: General symptom scales (Sickness Impact profile 8) – group-based CBT

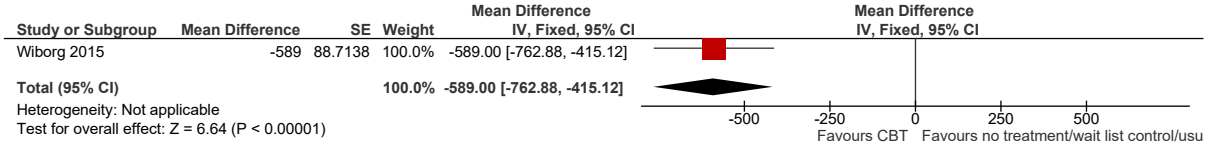

Figure 35: Fatigue/fatigability (Fatigue 0-10 scale) – individual face-to-face CBT

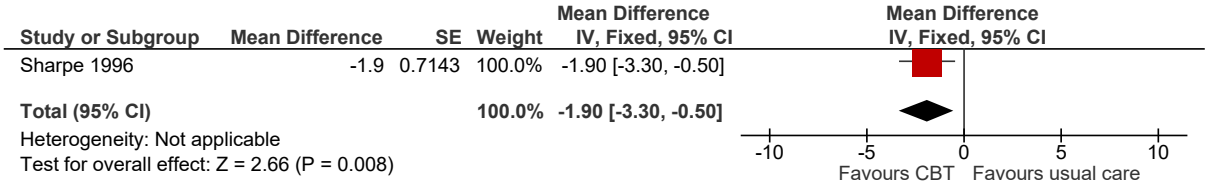

Figure 36: Fatigue/fatigability (Checklist individual strength - fatigue severity) – web/written CBT

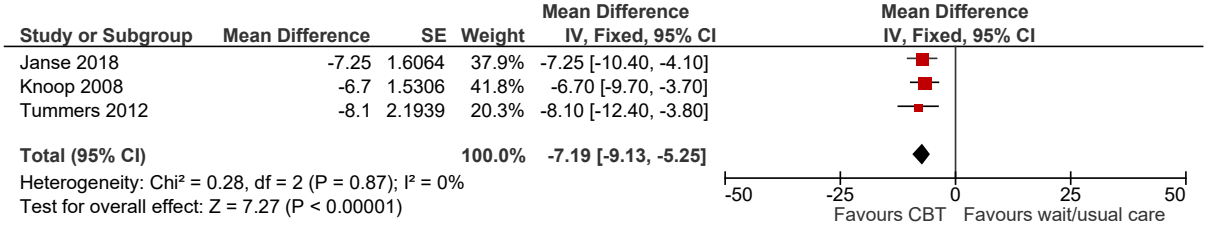

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Figure 37: Fatigue/fatigability (Checklist individual strength - fatigue severity) – group-based CBT

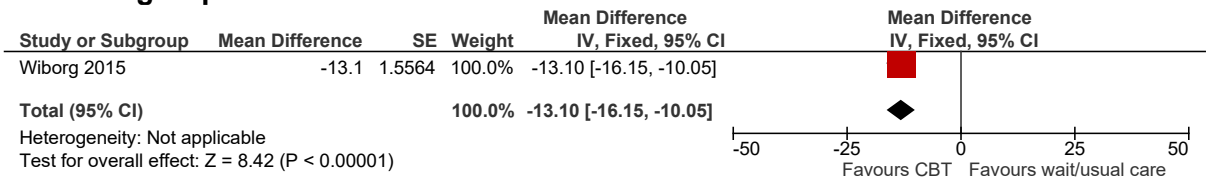

Figure 38: Fatigue/fatigability (Chalder fatigue questionnaire) – web/written CBT

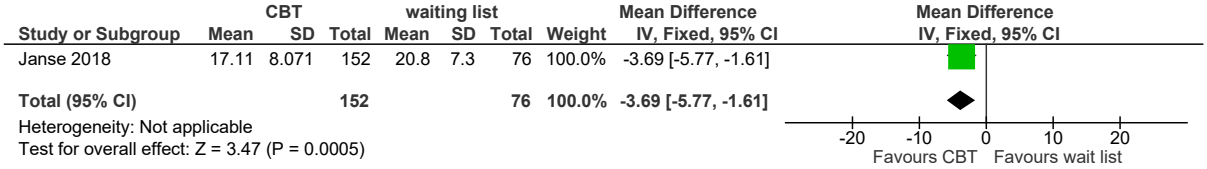

Figure 39: Fatigue/fatigability (Chalder fatigue questionnaire) – group-based CBT

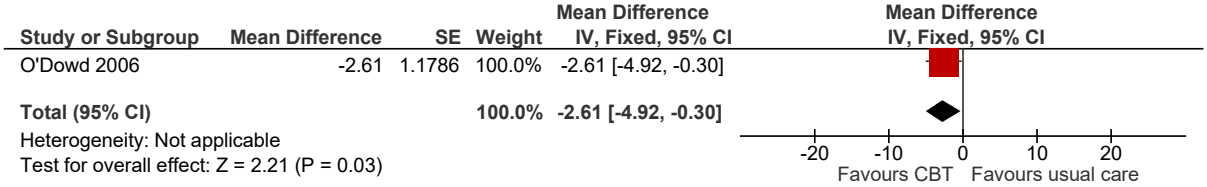

Figure 40: Fatigue (Chalder fatigue questionnaire) – individual face-to-face CBT

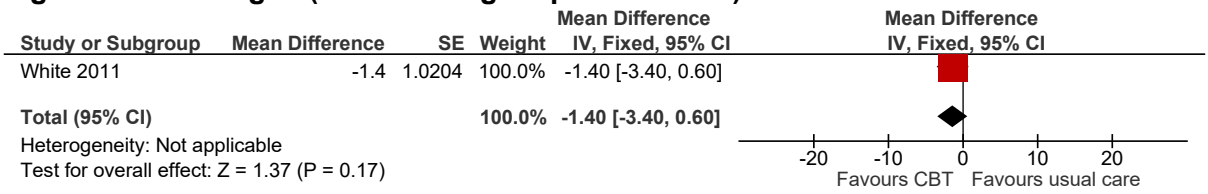

Figure 41: Physical functioning (SF36 physical functioning sub-scale) – web/written CBT

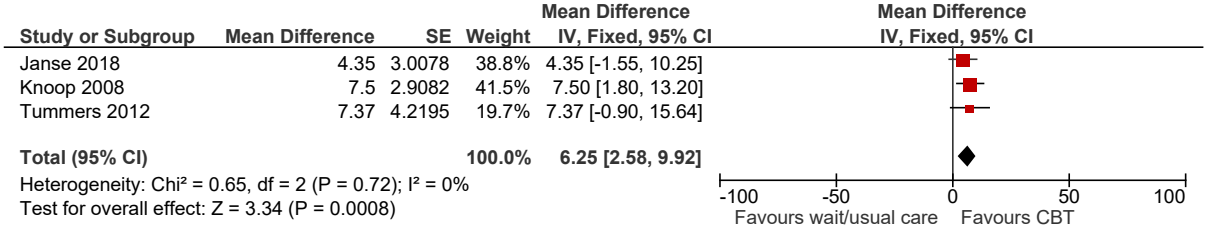

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Figure 42: Physical functioning (SF36 physical functioning sub-scale) – group-based CBT

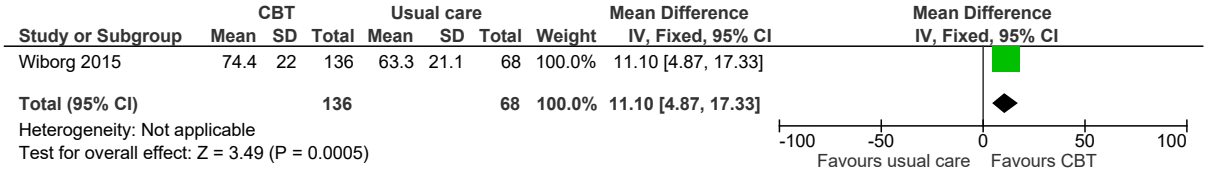

Figure 43: Physical functioning (SF36 physical function subscale) – individual face-to-face CBT

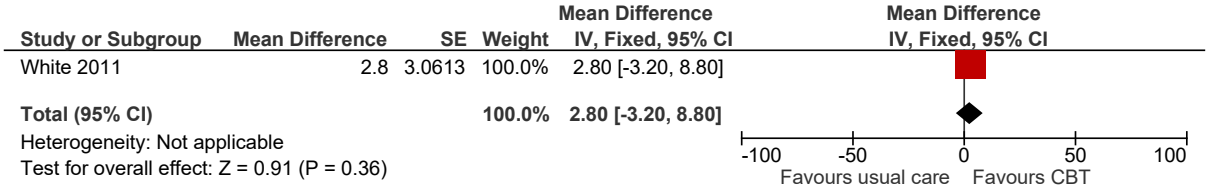

Figure 44: Cognitive function (total words recalled) – group-based CBT

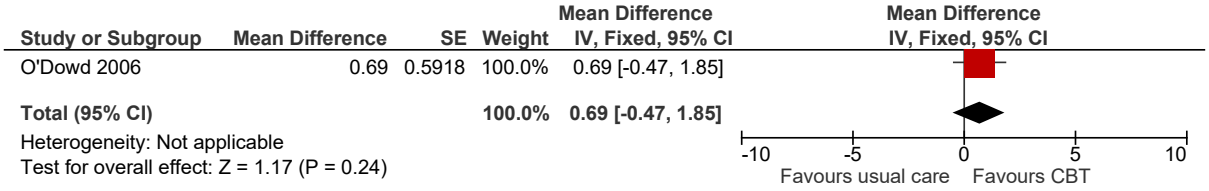

Figure 45: Cognitive function (reaction time) – group-based CBT

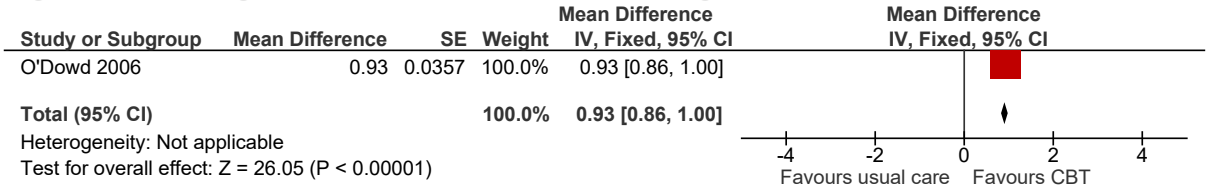

Figure 46: Cognitive function (correct words) – group-based CBT

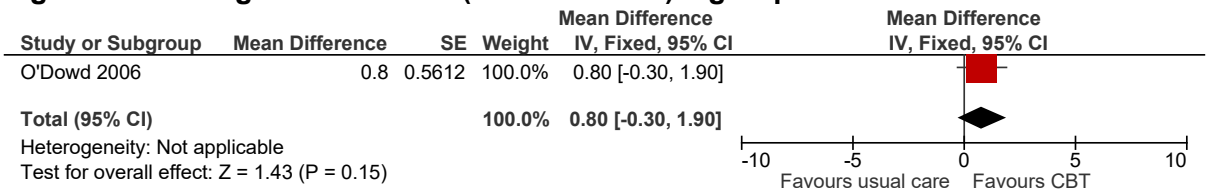

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Figure 47: Psychological status (Symptom Checklist 90 - psychological distress) – web/written CBT

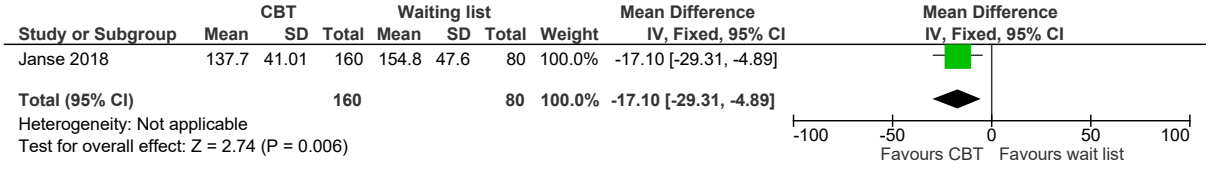

Figure 48: Psychological status (Symptom Checklist 90 - psychological distress) – group-based CBT

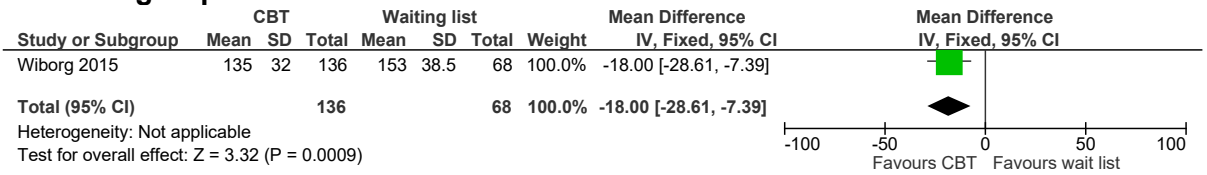

Figure 49: Psychological status (Brief Symptom Checklist) – web/written CBT

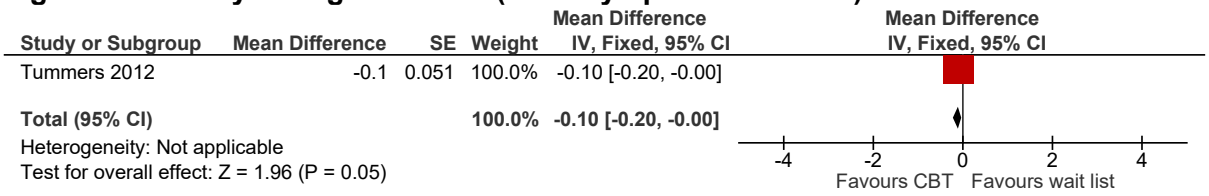

Figure 50: Psychological status (Hospital anxiety and depression scale - anxiety) – group-based CBT

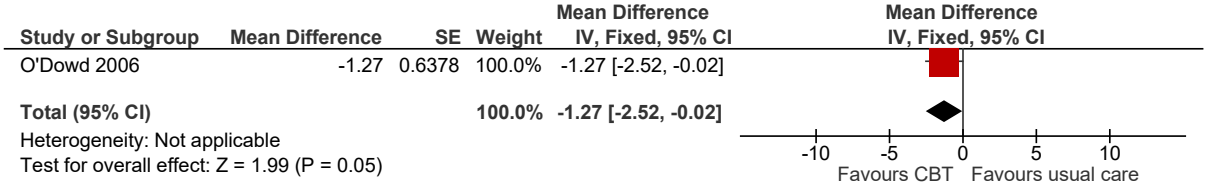

Figure 51: Psychological status (Hospital anxiety and depression scale - anxiety) – individual face-to-face CBT

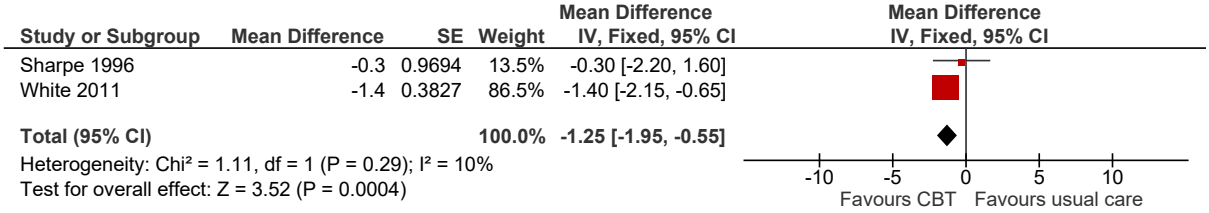

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Figure 52: Psychological status (Hospital anxiety and depression scale – depression) – group-based CBT

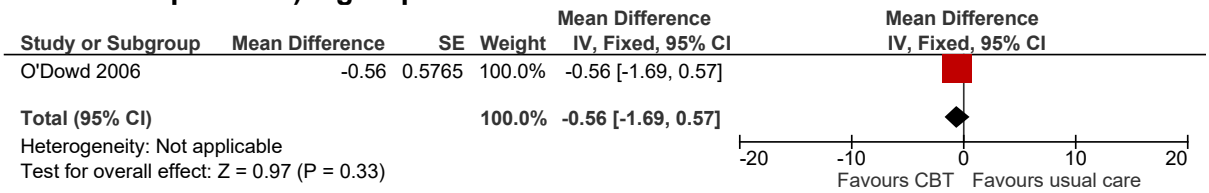

Figure 53: Psychological status (Hospital anxiety and depression scale – depression) – individual face-to-face CBT

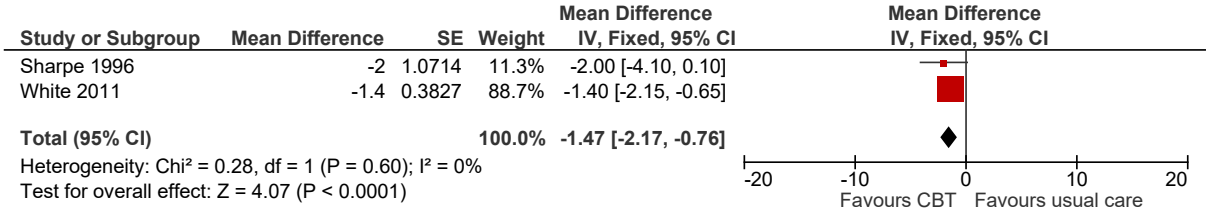

Figure 54: Psychological status (General health questionnaire) – group-based CBT

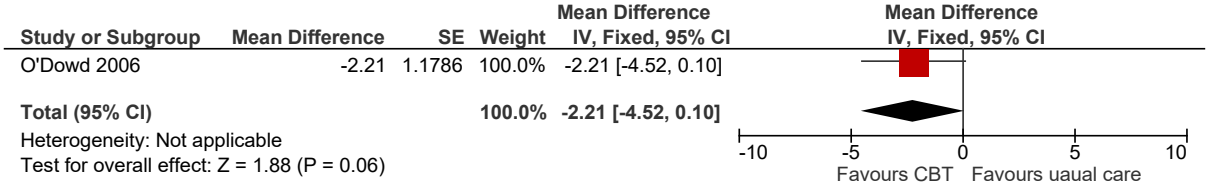

Figure 55: Pain (numeric rating scale) – individual face-to-face CBT

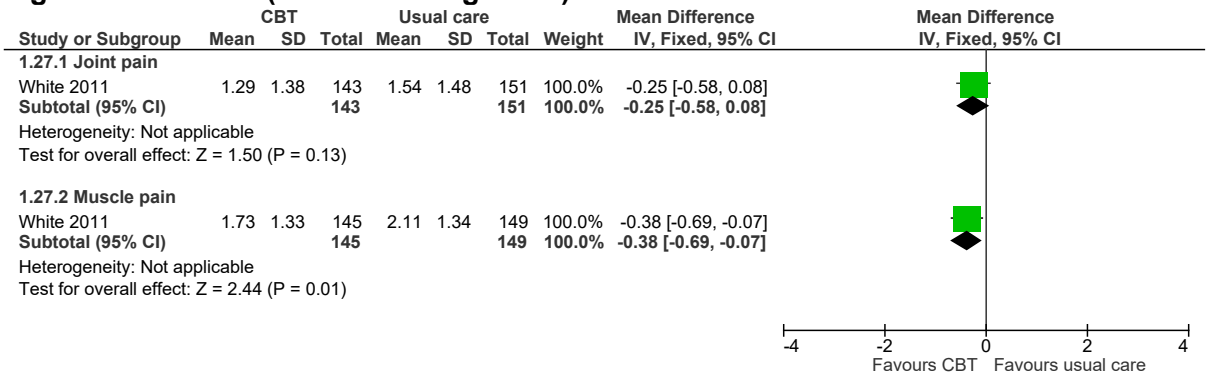

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Figure 56: Sleep quality (Jenkins sleep scale) – individual face-to-face CBT

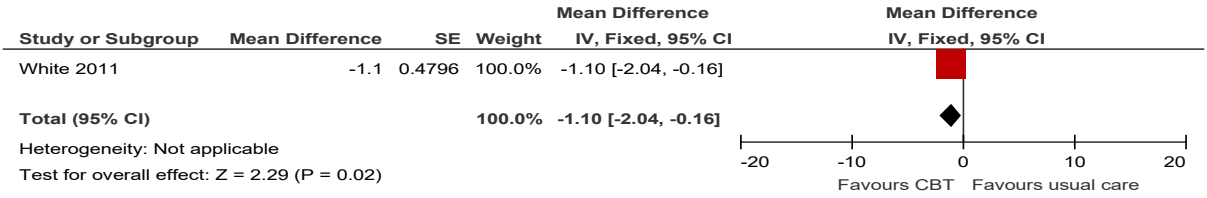

Figure 57: Adverse events – web/written CBT

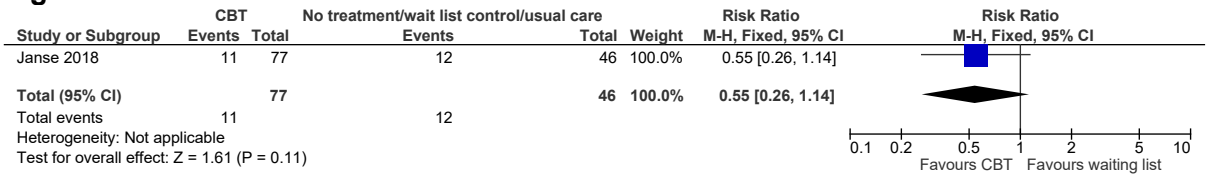

Figure 58: Adverse events (non-serious) – individual face-to-face CBT

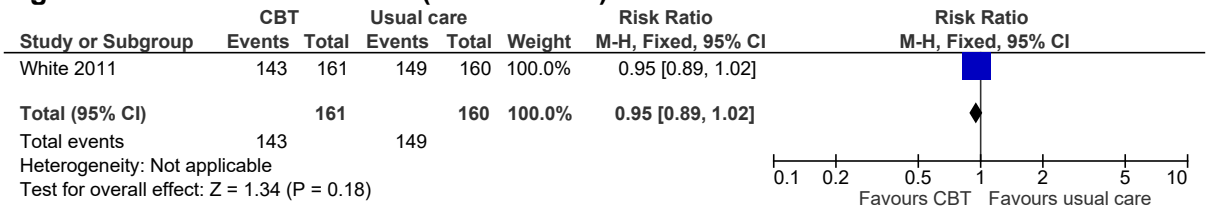

Figure 59: Adverse events (serious adverse events) – individual face-to-face CBT

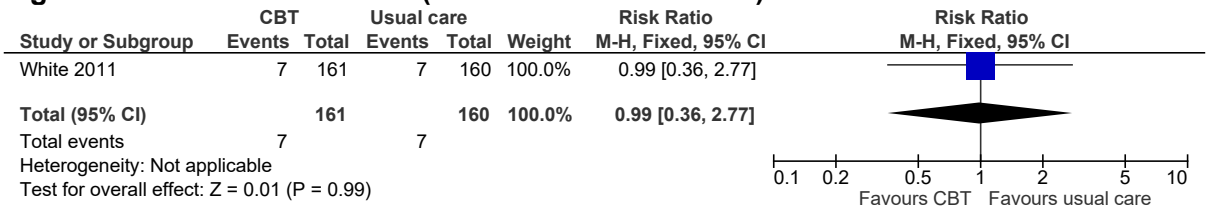

Figure 60: Adverse events (adverse reactions) – individual face-to-face CBT

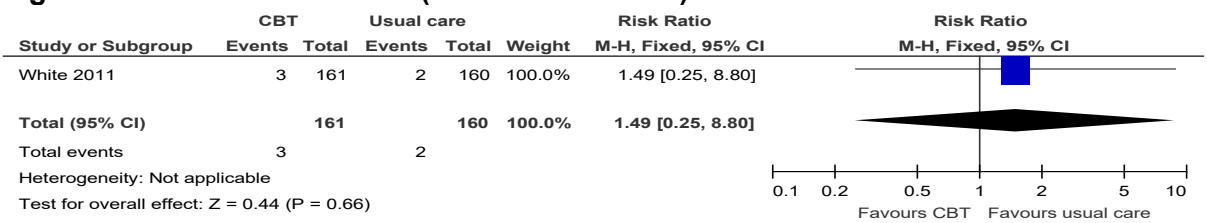

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Figure 61: Activity levels (Actigraphy mean score) – web/written CBT

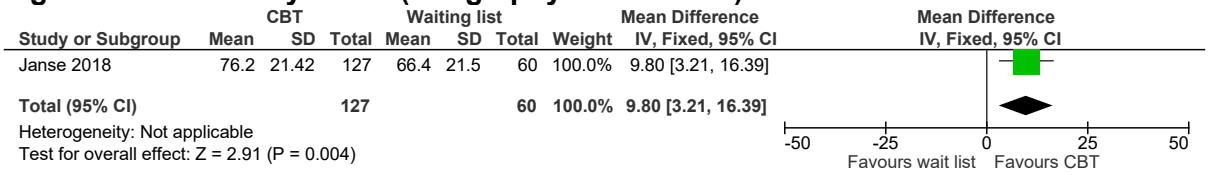

Figure 62: Activity levels (Number of days in bed per week) – individual face-to-face CBT

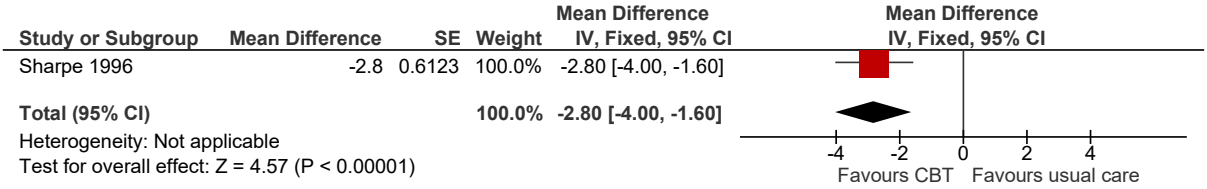

Figure 63: Activity levels (Percentage interference with activities) – individual face-to-face CBT

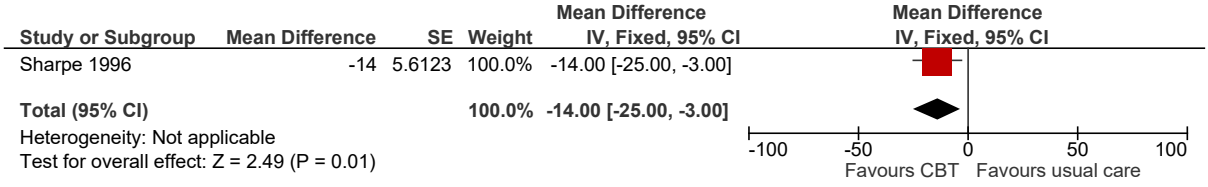

Figure 64: Return to school/work (Work and social adjustment scale) – web/written CBT

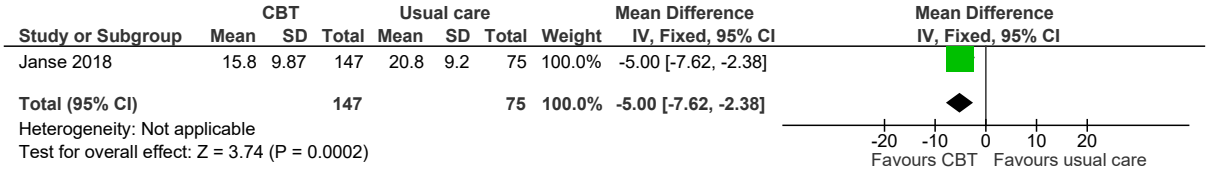

Figure 65: Return to school/work (Work and Social Adjustment Scale) – individual face-to-face CBT

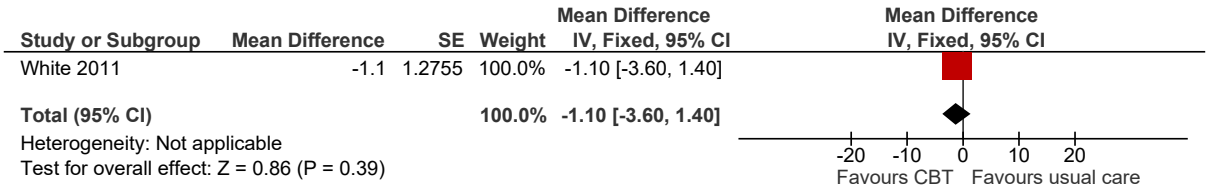

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Figure 66: Exercise performance measure (Normal walking speed) – group-based CBT

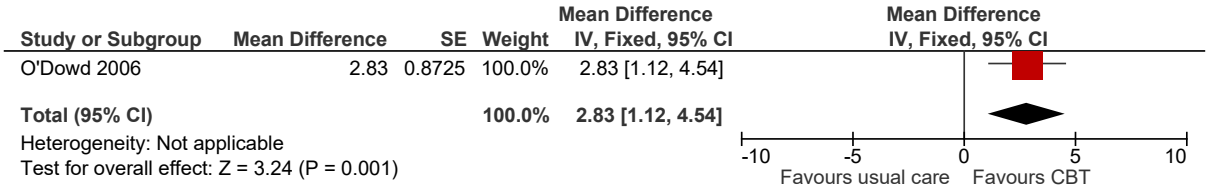


Figure 67: Exercise performance measure (Shuttles walked) – group-based CBT

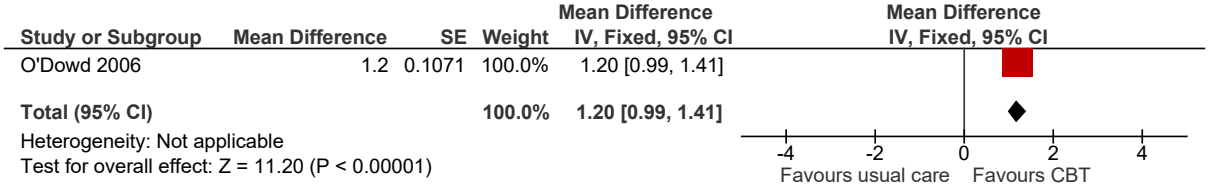


Figure 68: Exercise performance measure (Perceived fatigue- modified Borg scale)

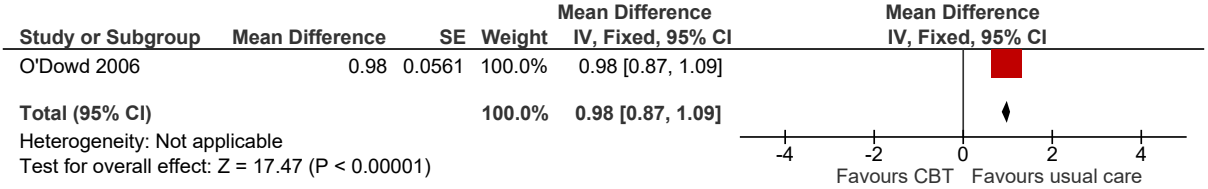
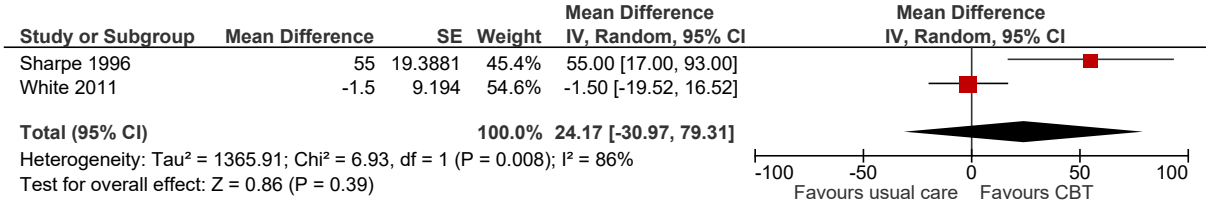


Figure 69: Exercise performance measure (6 min walk test) – individual face-to-face CBT



Source/Note: random effects applied where heterogeneity unexplained

E.2.2 Group-based cognitive behavioural stress management versus control (psycho-education): adults, severity mixed or unclear

Figure 70: Quality of life (Quality of Life Inventory)

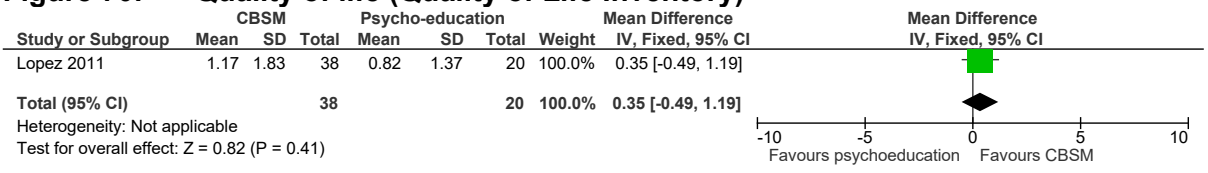


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Figure 71: General symptom scales (CDC Symptom Inventory)

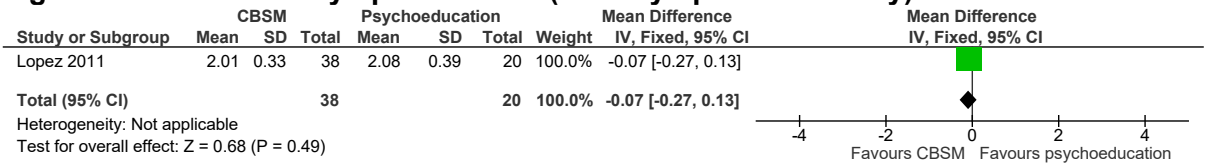


Figure 72: Psychological status (Profile of Mood States - total mood disturbance)

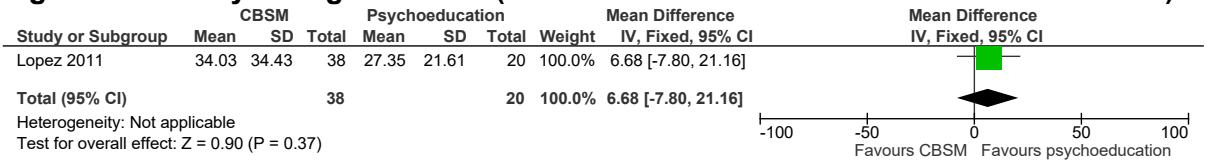
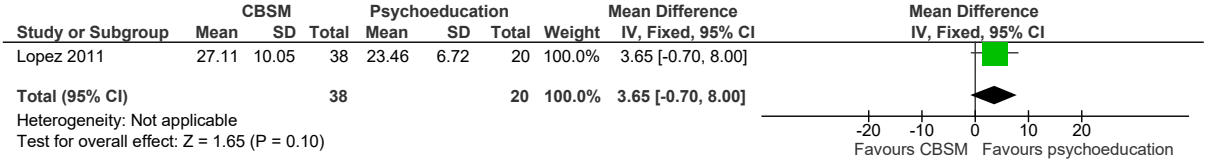


Figure 73: Psychological status (Perceived Stress Scale)



E.2.3 Group-based cognitive behavioural therapy versus education and support group: adults, severity mixed or unclear

Figure 74: Quality of life (SF36)

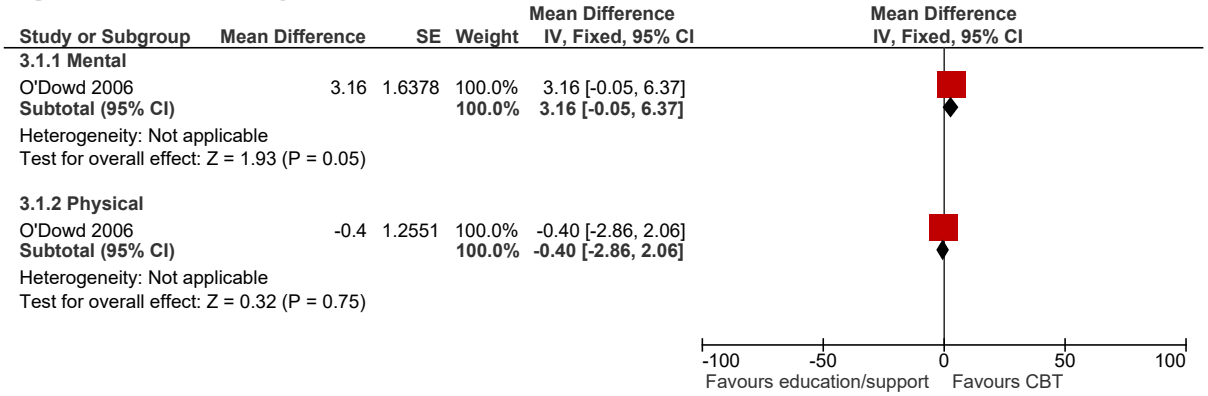


Figure 75: Quality of life (Health status (HUI3))

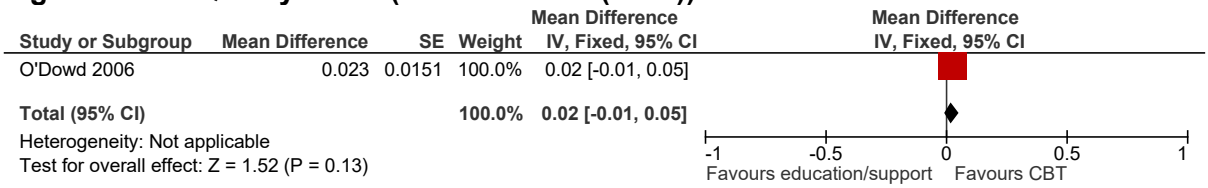


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Figure 76: Fatigue (Chalder fatigue scale)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	-3.16	1.2398	100.0%	-3.16 [-5.59, -0.73]
Total (95% CI)			**100.0%**	**-3.16 [-5.59, -0.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)

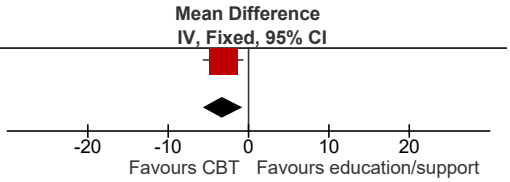

Figure 77: Cognitive function (total words recalled)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	0.77	0.5561	100.0%	0.77 [-0.32, 1.86]
Total (95% CI)			**100.0%**	**0.77 [-0.32, 1.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

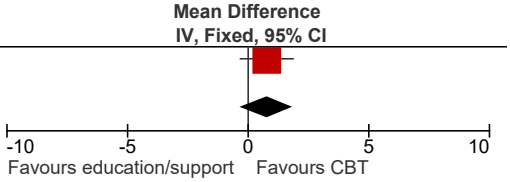

Figure 78: Cognitive function (correct words)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	0.84	0.5612	100.0%	0.84 [-0.26, 1.94]
Total (95% CI)			**100.0%**	**0.84 [-0.26, 1.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)

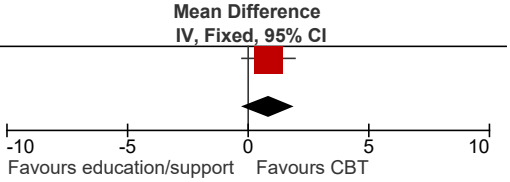

Figure 79: Cognitive function (reaction time)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	0.99	0.0459	100.0%	0.99 [0.90, 1.08]
Total (95% CI)			**100.0%**	**0.99 [0.90, 1.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 21.57 (P < 0.00001)

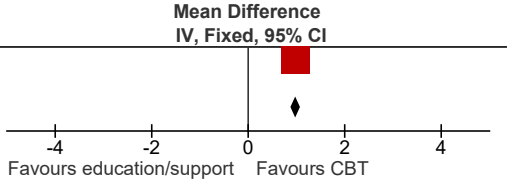

Figure 80: Psychological status (HADS anxiety)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
O'Dowd 2006	-0.51	0.6072	100.0%	-0.51 [-1.70, 0.68]
Total (95% CI)			**100.0%**	**-0.51 [-1.70, 0.68]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

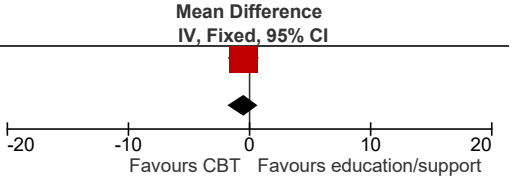

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Figure 81: Psychological status (HADS depression)

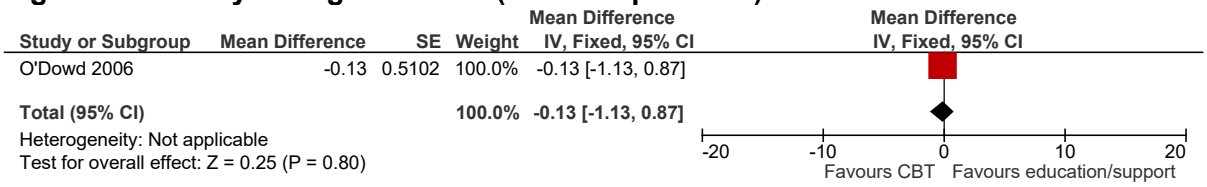


Figure 82: Psychological status (General health Questionnaire)

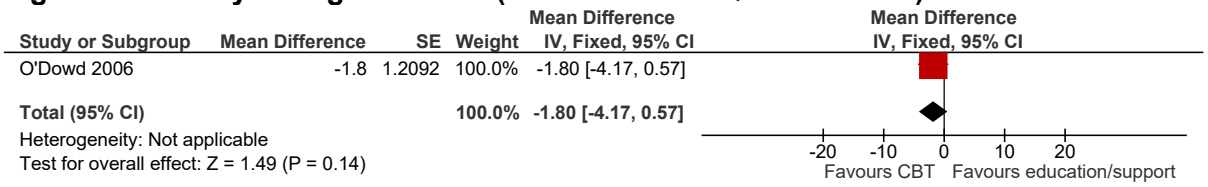


Figure 83: Exercise performance measure (Normal walking speed)

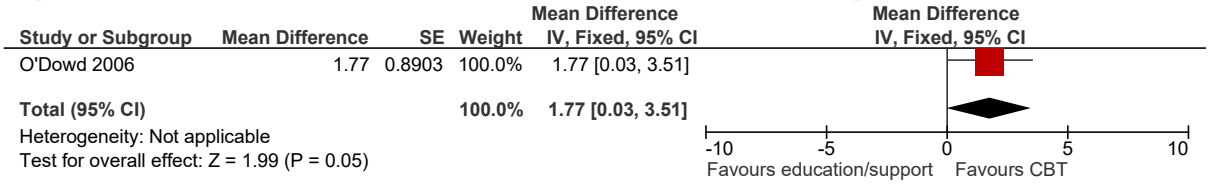


Figure 84: Exercise performance measure (Shuttles walked)

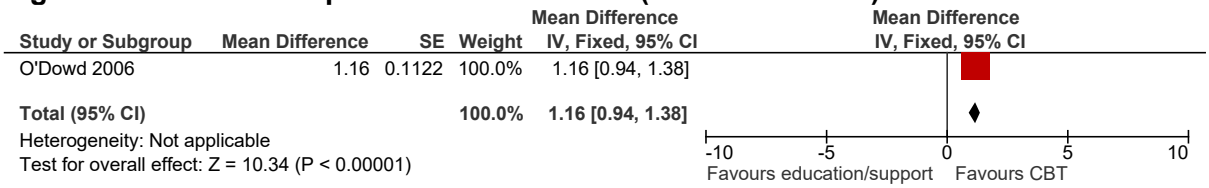
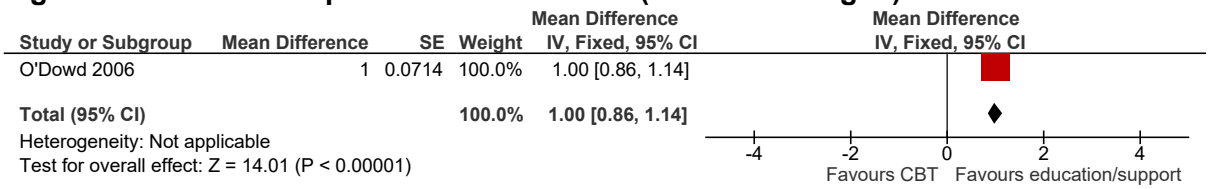


Figure 85: Exercise performance measure (Perceived fatigue)



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E.2.4 Individual face-to-face cognitive behavioural therapy versus multidisciplinary rehabilitation: adults, severity mixed or unclear

Figure 86: Quality of life (SF36)

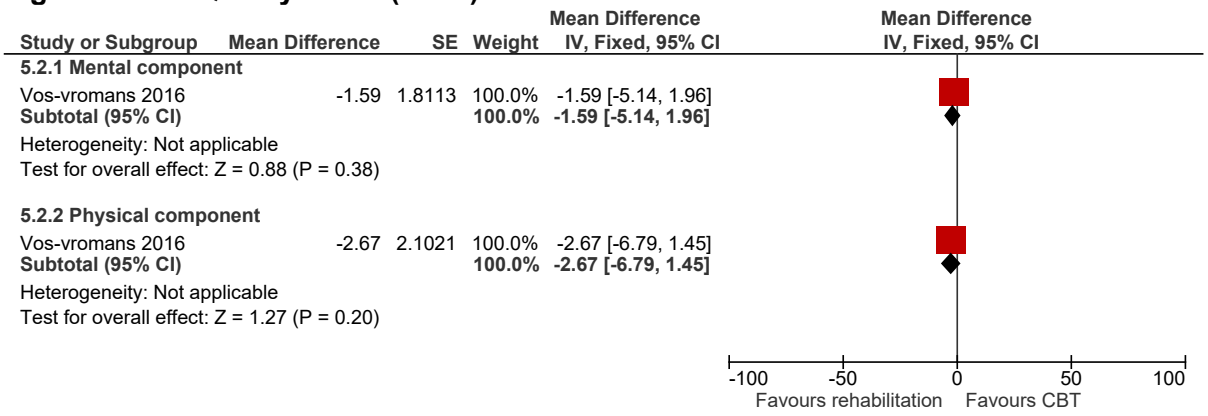

Figure 87: General symptom scales (Sickness Impact Profile 8)

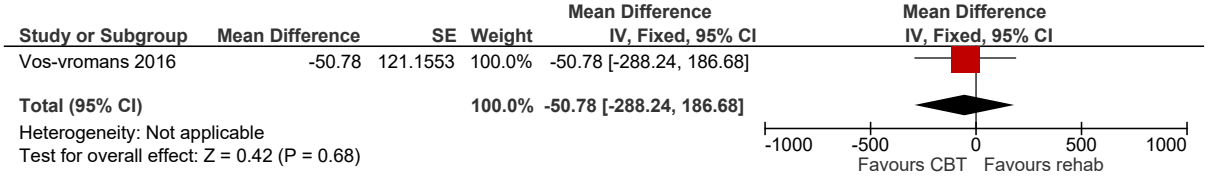

Figure 88: Fatigue (Checklist Individual Strength - fatigue severity)

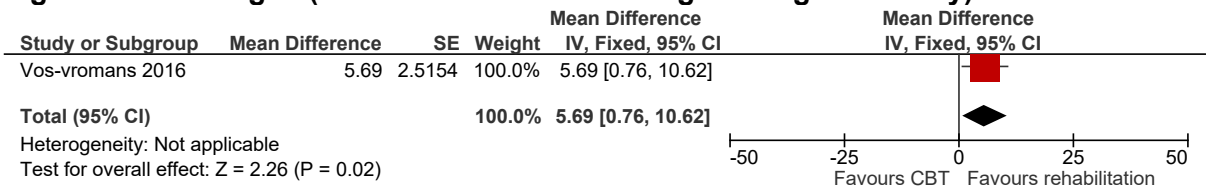

Figure 89: Psychological status (Symptom Checklist 90)

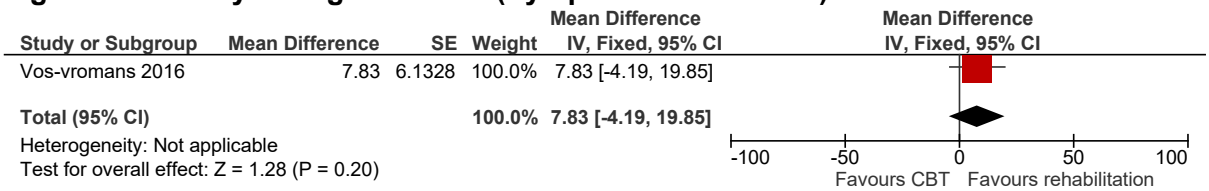

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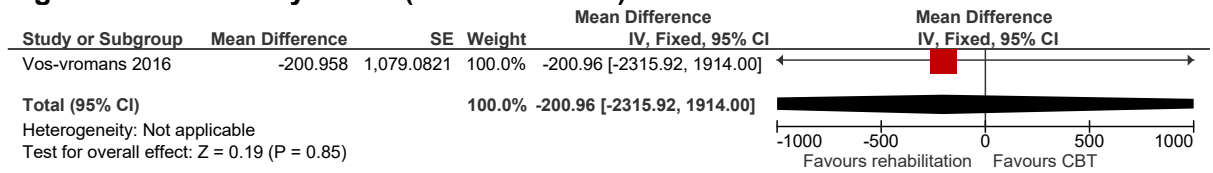
Figure 90: Activity levels (Accelerometer)



Source/Note: Values have been divided by one decimal place in order to display the effect estimate

E.2.5 Individual face-to-face cognitive behavioural therapy versus relaxation: adults, severity mixed or unclear

Figure 91: General symptom scales (self-rating of better/much better)

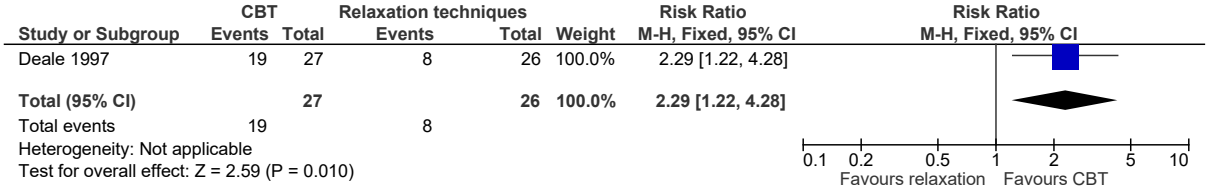


Figure 92: General symptom scales (self-rating of much/very much better) at 5 years

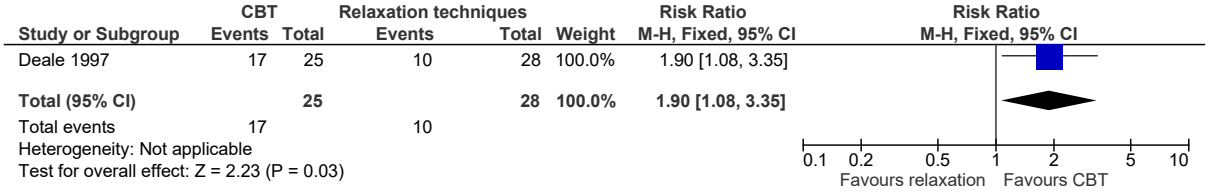


Figure 93: Fatigue (Chalder Fatigue questionnaire)

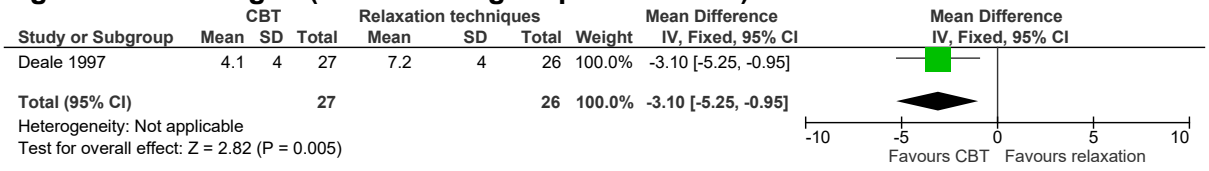


Figure 94: Fatigue/fatigability (Fatigue problem rating)

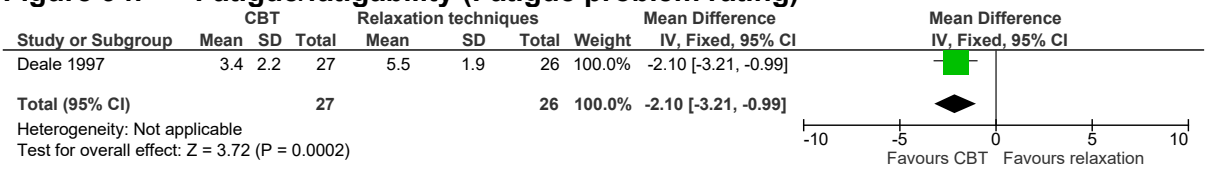


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Figure 95: Physical functioning (short form general health survey physical functioning scale

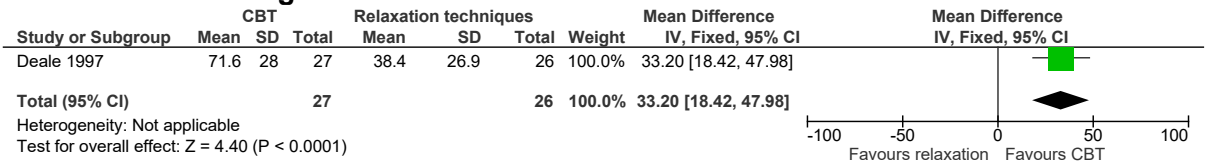


Figure 96: Psychological status (Beck depression inventory)

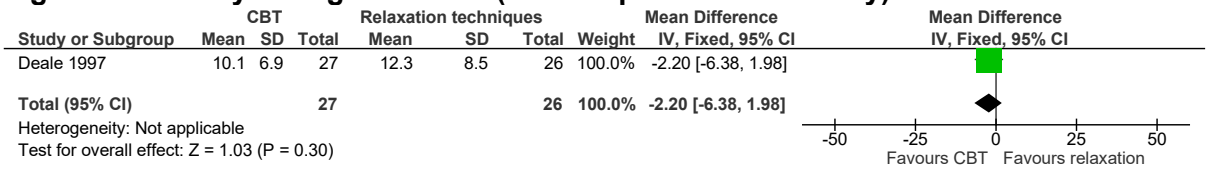


Figure 97: Psychological status (General health questionnaire - 12 item)

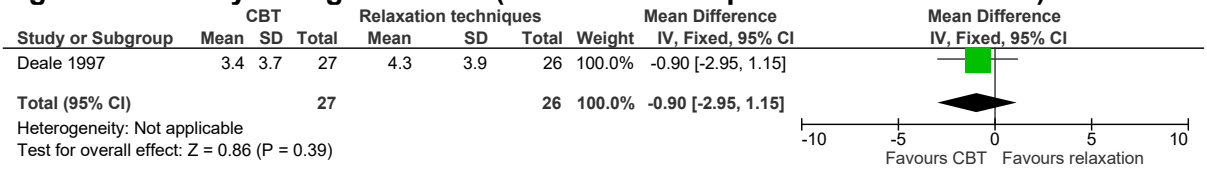


Figure 98: Return to school or work (Full or part time employment at 5 years)

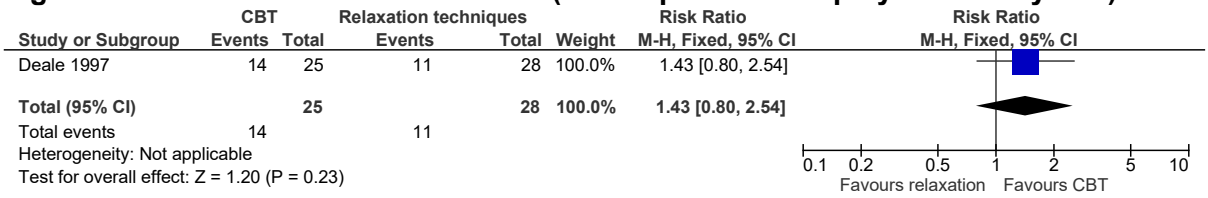
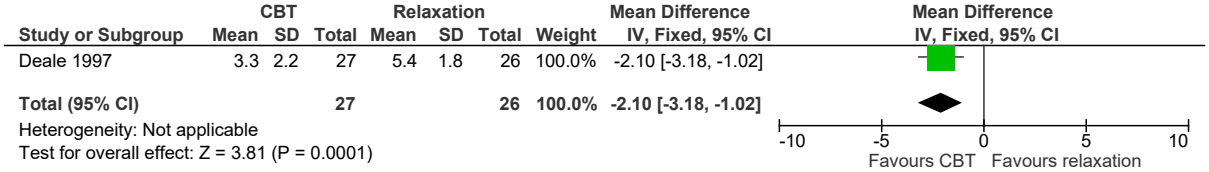


Figure 99: Return to school or work (Work and social adjustment scale)



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E.2.6 Individual face-to-face cognitive behavioural therapy versus adaptive pacing therapy: adults, severity mixed or unclear

Figure 100: Quality of life (EQ5D)

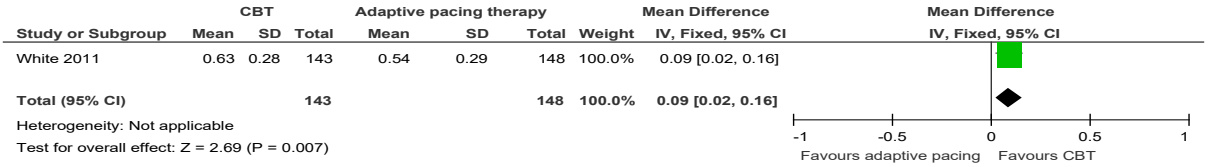

Figure 101: General symptoms scales: Clinical Global Impression scale - proportion with positive change (very much better or much better)

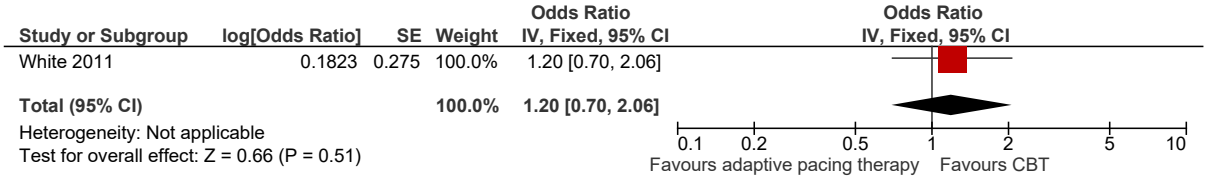

Figure 102: Fatigue (Chalder fatigue questionnaire)

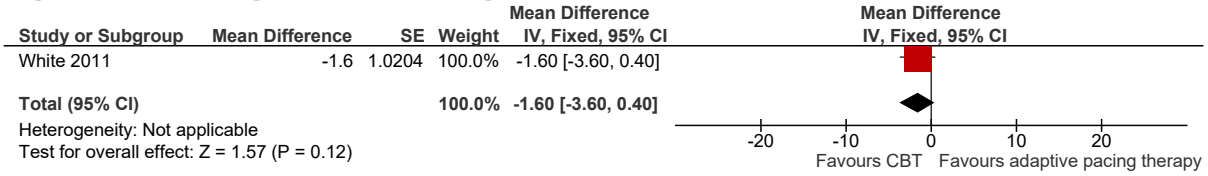

Figure 103: Physical functioning (SF-36 physical function subscale)

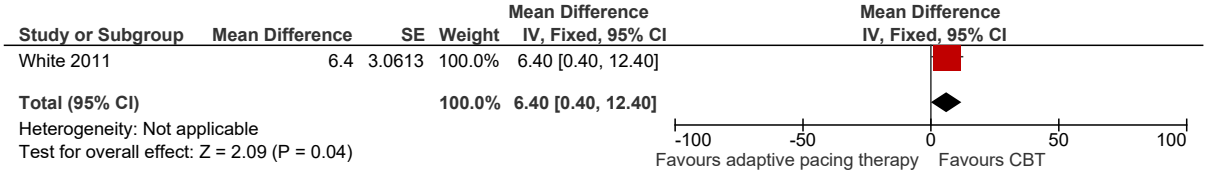

Figure 104: Psychological status (HADS anxiety scale)

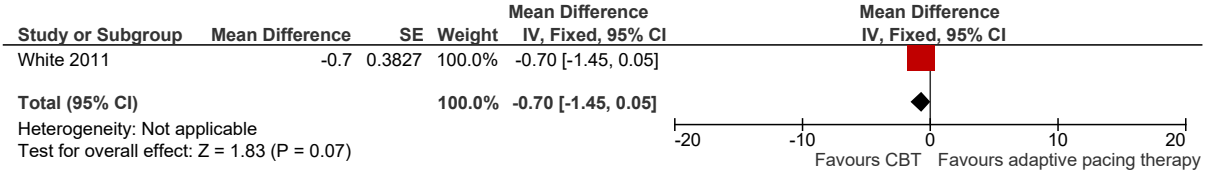

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Figure 105: Psychological status (HADS depression scale)

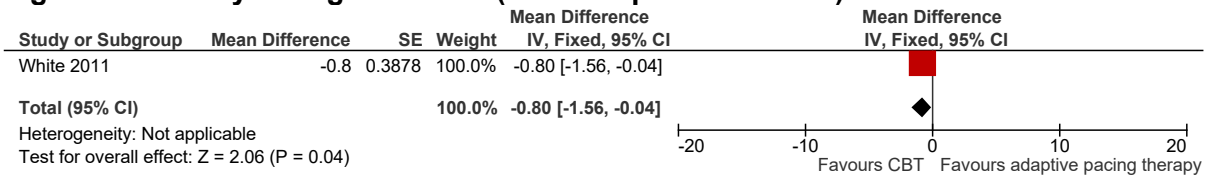

Figure 106: Pain (muscle pain numeric rating scale)

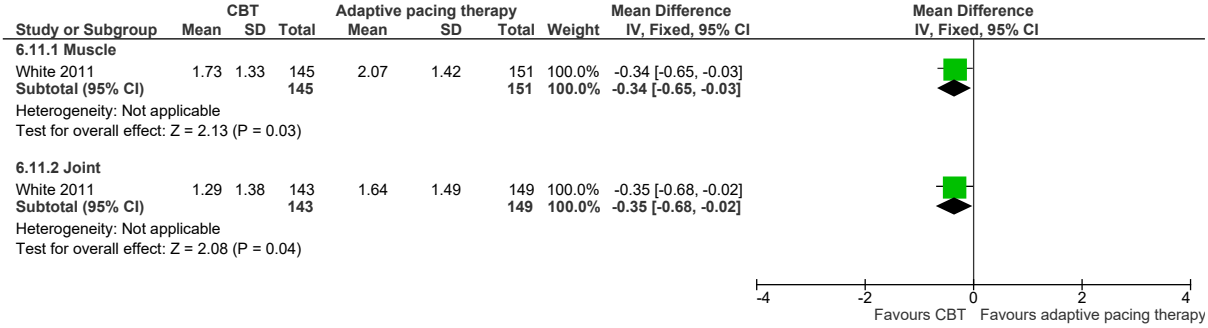

Figure 107: Sleep quality (Jenkins sleep scale)

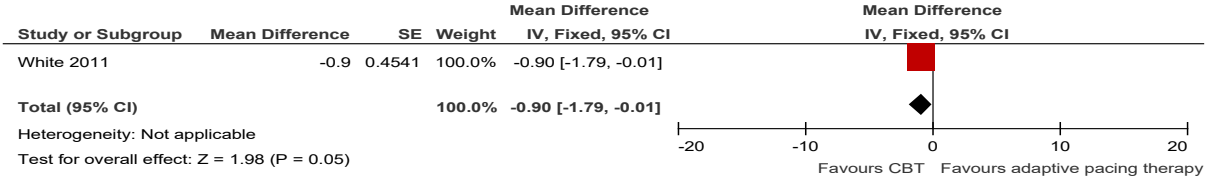

Figure 108: Adverse events (non-serious)

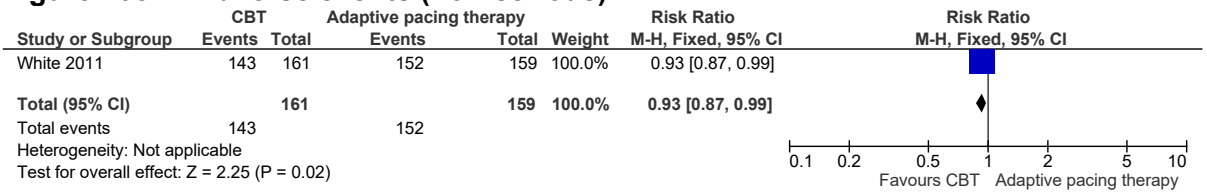

Figure 109: Adverse events (serious)

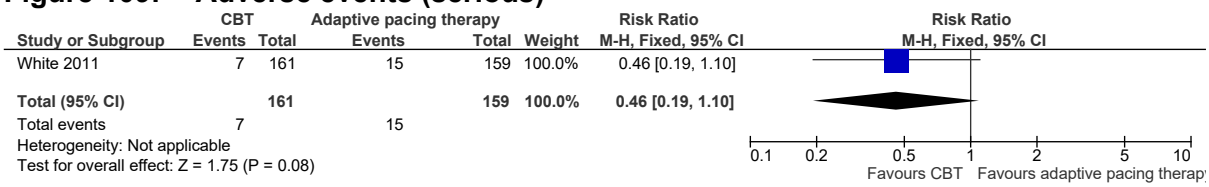

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Figure 110: Adverse events (adverse reactions)

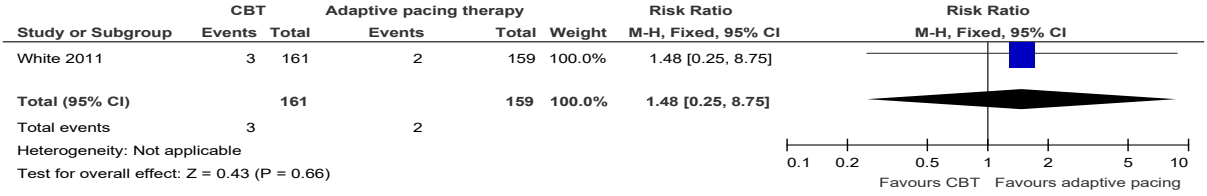


Figure 111: Return to school/work (Work and Social Adjustment Scale)

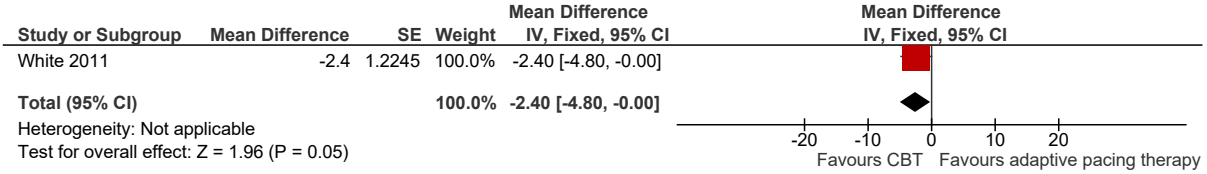
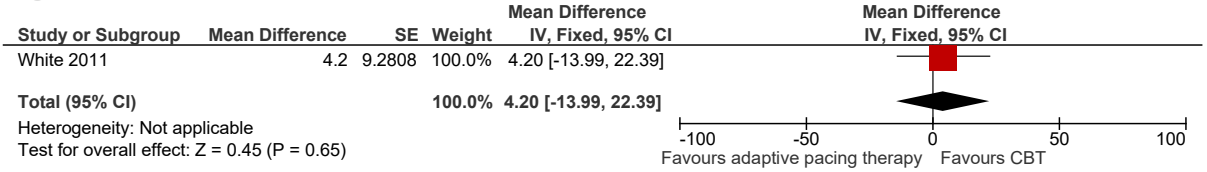


Figure 112: Exercise performance measure (6 min walk test)



E.2.7 Individual face-to-face cognitive behavioural therapy versus graded exercise therapy: adults, severity mixed or unclear

Figure 113: Quality of life (EQ5D)

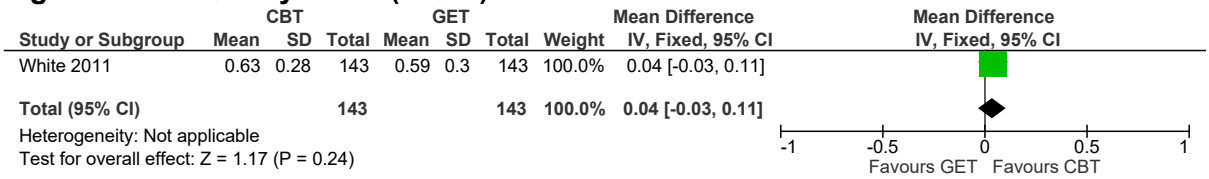


Figure 114: General symptoms scales (Clinical Global Impression Scale - positive change (very much better or much better))

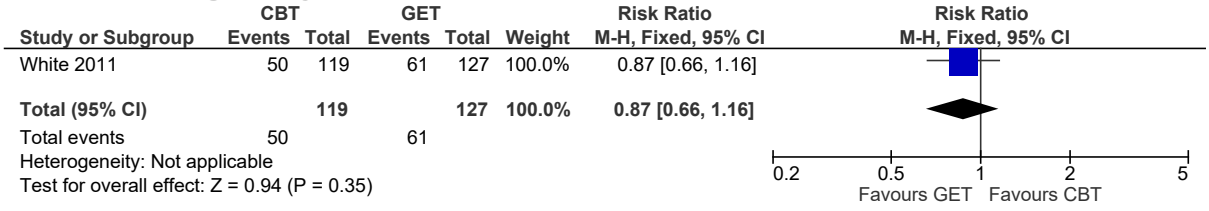


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Figure 115: Fatigue (Chalder fatigue questionnaire)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	GET Mean	GET SD	GET Total	Weight	Mean Difference IV, Fixed, 95% CI
White 2011	18.4	8.5	119	19.1	7.9	127	100.0%	-0.70 [-2.75, 1.35]
Total (95% CI)			**119**			**127**	**100.0%**	**-0.70 [-2.75, 1.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

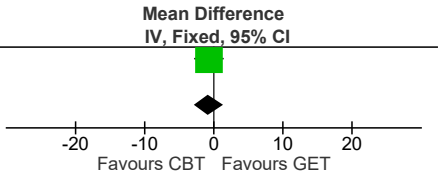

Figure 116: Physical functioning (SF-36 physical function subscale)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	GET Mean	GET SD	GET Total	Weight	Mean Difference IV, Fixed, 95% CI
White 2011	62.2	27.2	119	59.8	27.6	127	100.0%	2.40 [-4.45, 9.25]
Total (95% CI)			**119**			**127**	**100.0%**	**2.40 [-4.45, 9.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

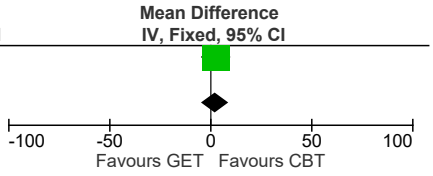

Figure 117: Psychological status (HADS anxiety scale)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	GET Mean	GET SD	GET Total	Weight	Mean Difference IV, Fixed, 95% CI
White 2011	6.8	4.2	143	7.1	4.5	144	100.0%	-0.30 [-1.31, 0.71]
Total (95% CI)			**143**			**144**	**100.0%**	**-0.30 [-1.31, 0.71]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

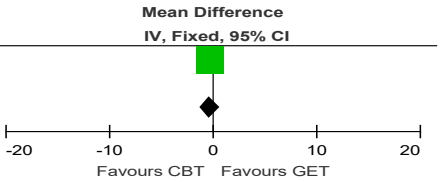

Figure 118: Psychological status (HADS depression scale)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	GET Mean	GET SD	GET Total	Weight	Mean Difference IV, Fixed, 95% CI
White 2011	6.2	3.7	143	6.1	4.1	144	100.0%	0.10 [-0.80, 1.00]
Total (95% CI)			**143**			**144**	**100.0%**	**0.10 [-0.80, 1.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

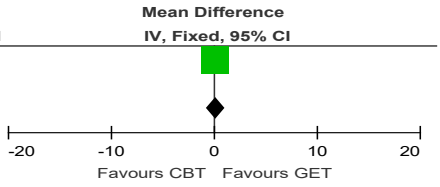

Figure 119: Pain (muscle pain numeric rating scale)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	GET Mean	GET SD	GET Total	Weight	Mean Difference IV, Fixed, 95% CI
7.11.1 Muscle								
White 2011	1.73	1.33	145	1.69	1.38	144	100.0%	0.04 [-0.27, 0.35]
Subtotal (95% CI)			**145**			**144**	**100.0%**	**0.04 [-0.27, 0.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

7.11.2 Joint								
White 2011	1.29	1.38	143	1.28	1.32	144	100.0%	0.01 [-0.30, 0.32]
Subtotal (95% CI)			**143**			**144**	**100.0%**	**0.01 [-0.30, 0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)

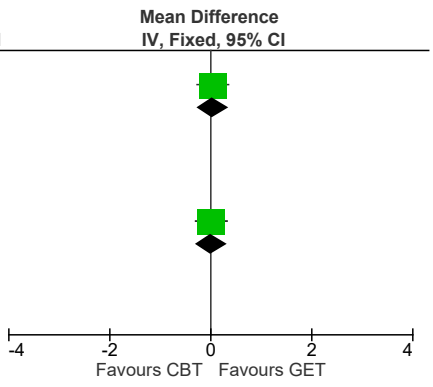

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Figure 120: Sleep quality (Jenkins sleep scale)

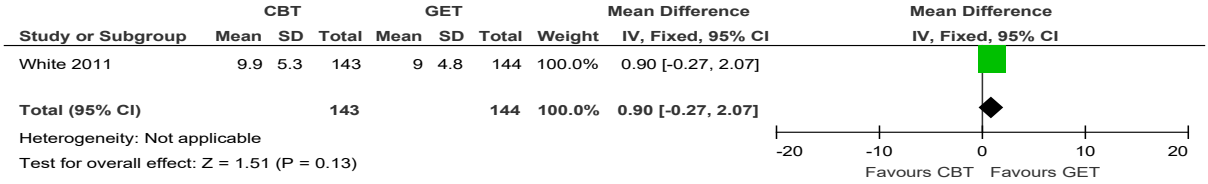

Figure 121: Adverse events (non-serious)

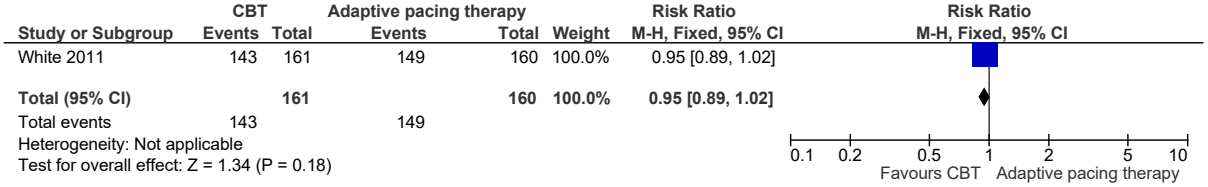

Figure 122: Adverse events (serious)

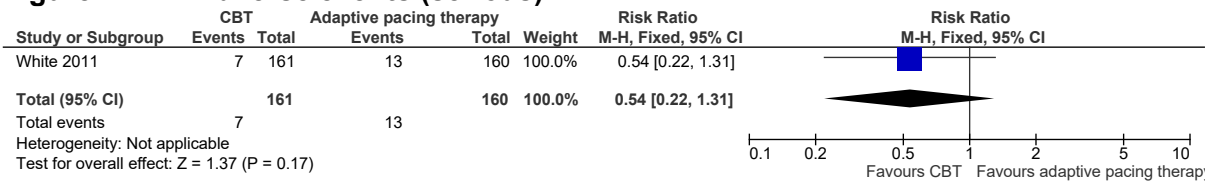

Figure 123: Adverse events (adverse reactions)

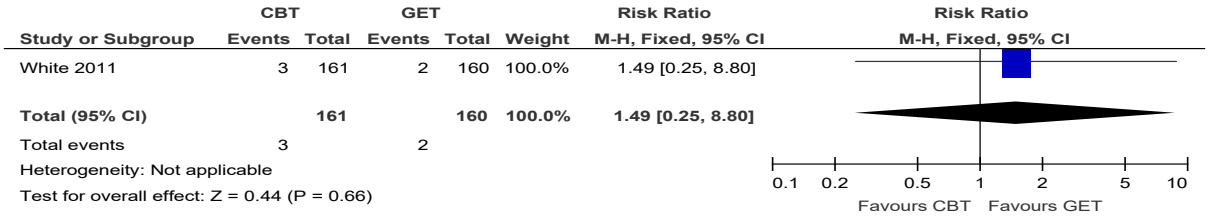

Figure 124: Return to school/work (Work and social adjustment scale)

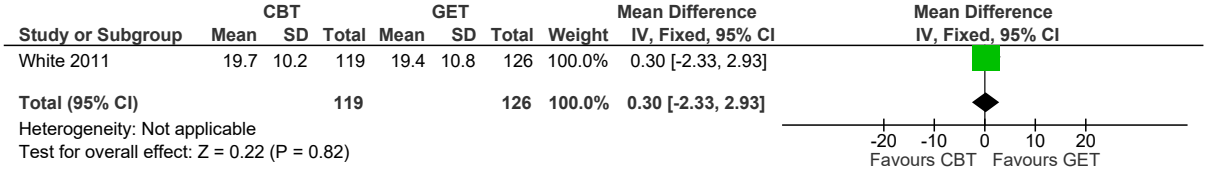

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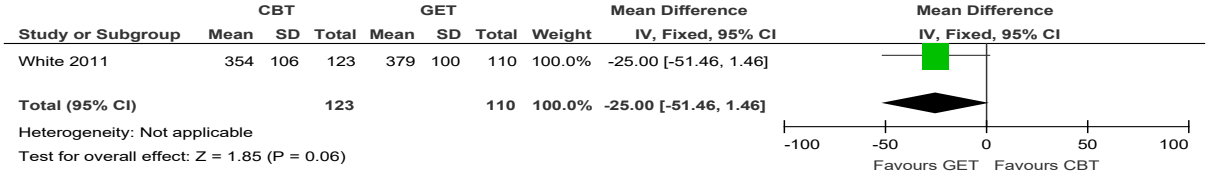
Figure 125: Exercise performance measure (6 min walk test)



E.2.8 Group-based cognitive behavioural therapy + graded exercise therapy versus usual care: age and severity mixed or unclear

Figure 126: Quality of life (SF36)

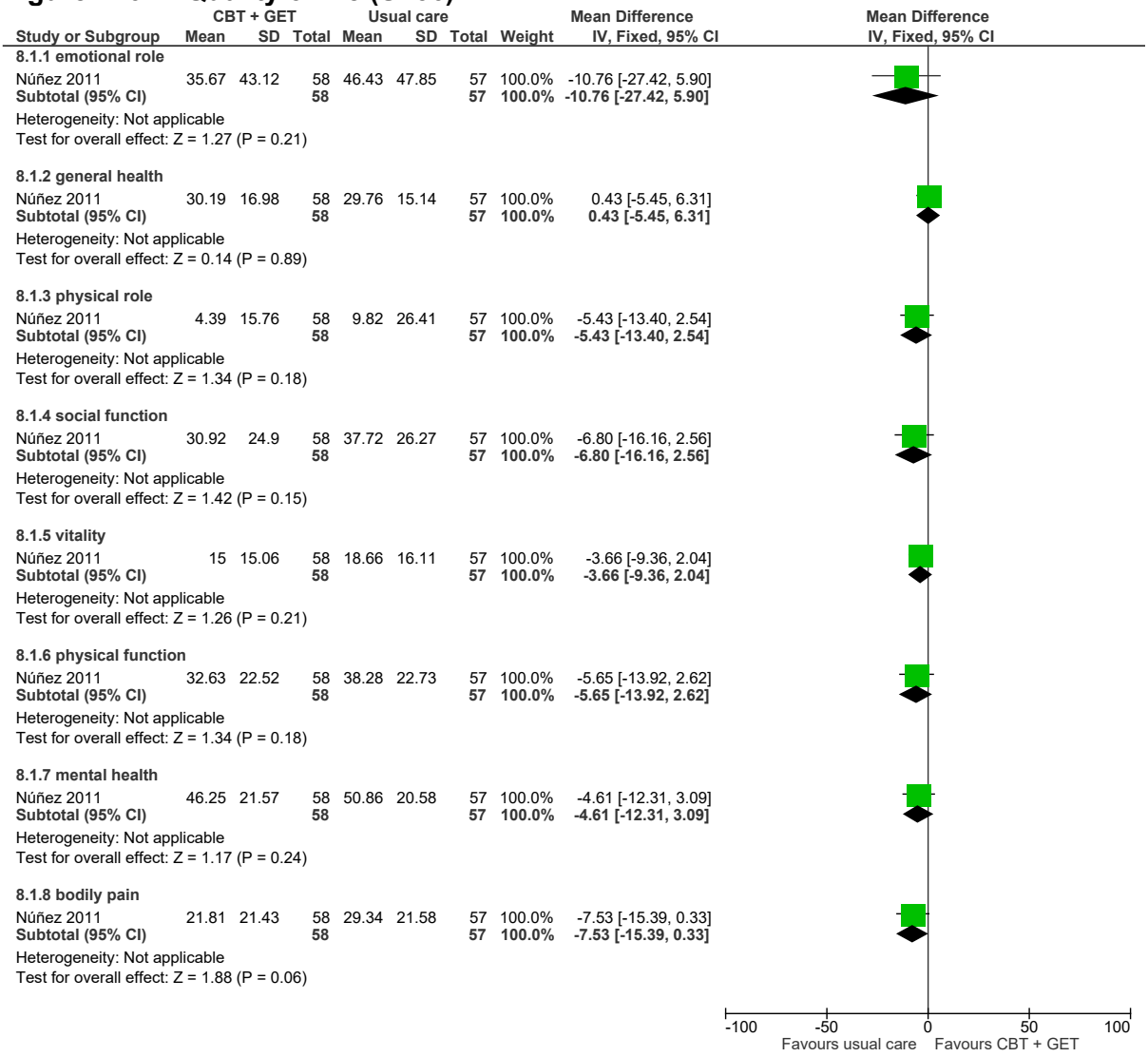


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Figure 127: General symptom scales (Stanford Health Assessment Questionnaire - global health status)

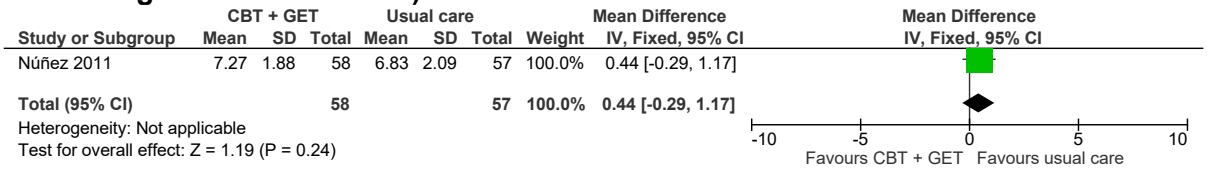


Figure 128: Physical functioning (Stanford Health Assessment Questionnaire)

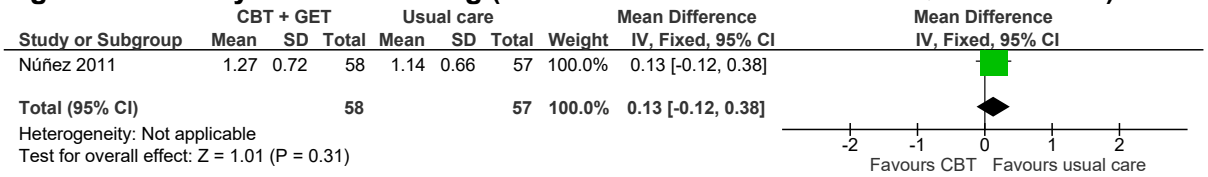
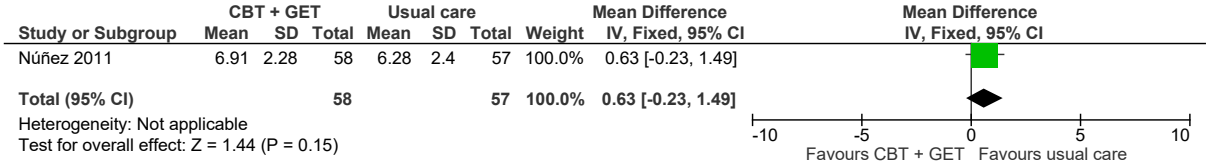


Figure 129: Pain (Stanford Health Assessment Questionnaire - pain intensity)



E.2.9 Individual face-to-face cognitive behavioural therapy versus counselling: age and severity mixed or unclear

Figure 130: Fatigue (Chalder fatigue scale)

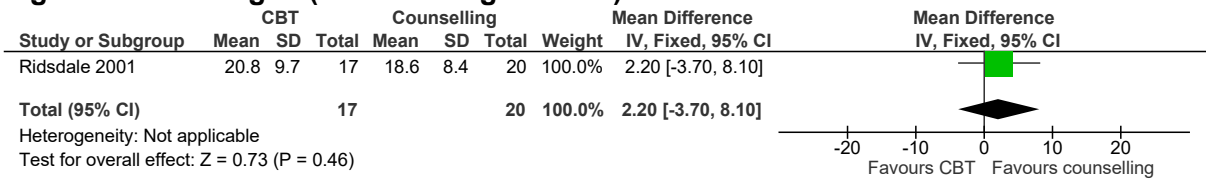


Figure 131: Psychological status (Hospital Anxiety and Depression Scale – anxiety)

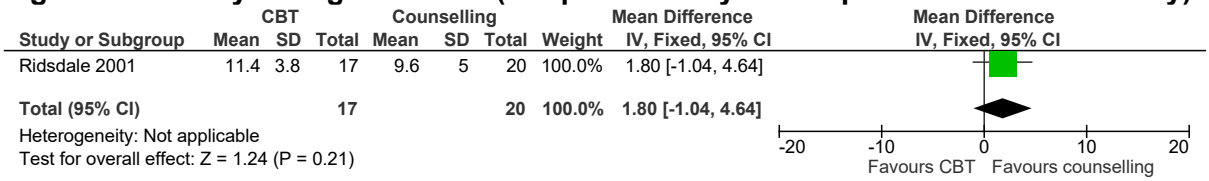


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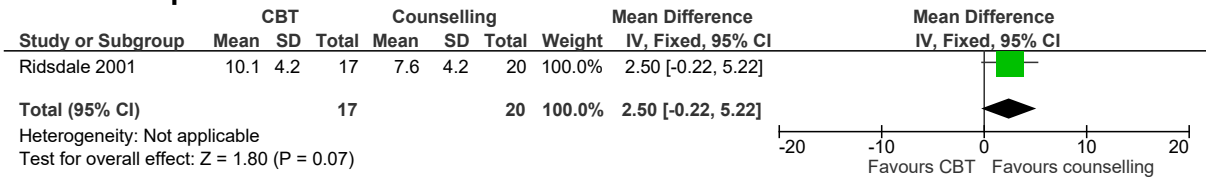
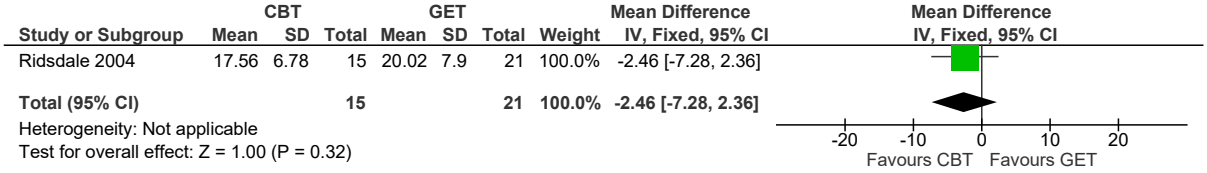
Figure 132: Psychological status (Hospital Anxiety and Depression Scale – depression



E.2.10 Individual face-to-face cognitive behavioural therapy versus graded exercise therapy: age and severity mixed or unclear

Figure 133: Fatigue (Chalder fatigue scale)



E.2.11 Individual face-to-face cognitive behavioural therapy versus relaxation: adults, moderate severity

Figure 134: Quality of life (Quality of Life Scale)

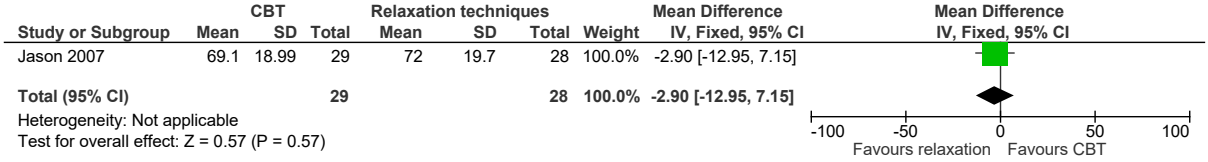


Figure 135: General symptom scales (self-rated global impression of change improved/much improved/very much improved)

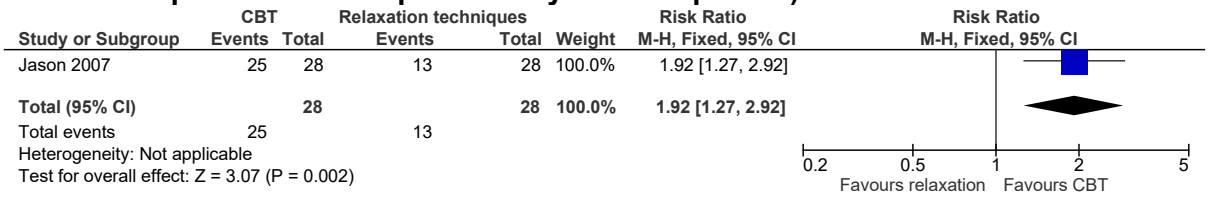


Figure 136: Fatigue (Fatigue Severity Scale)

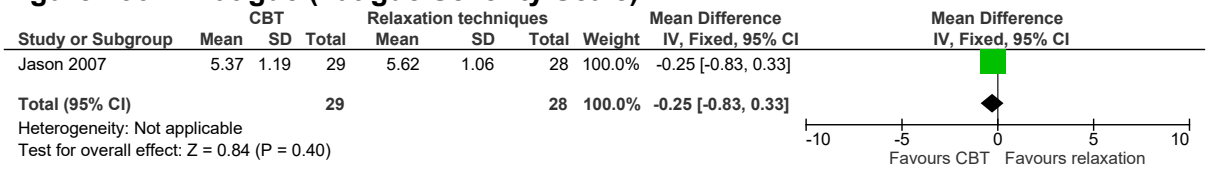


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Figure 137: Physical functioning (SF36 physical functioning)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Relaxation techniques Mean	Relaxation techniques SD	Relaxation techniques Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	58.64	30.44	29	61.2	27.7	28	100.0%	-2.56 [-17.66, 12.54]
Total (95% CI)			**29**			**28**	**100.0%**	**-2.56 [-17.66, 12.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

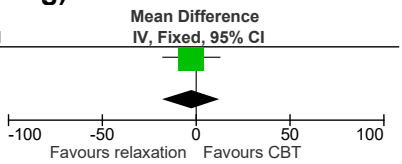

Figure 138: Psychological status (Beck depression inventory)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Relaxation techniques Mean	Relaxation techniques SD	Relaxation techniques Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	13.95	13.08	29	13.5	9.97	28	100.0%	0.45 [-5.57, 6.47]
Total (95% CI)			**29**			**28**	**100.0%**	**0.45 [-5.57, 6.47]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

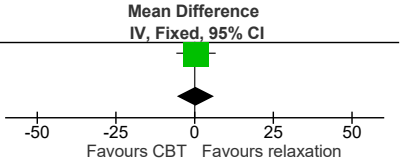

Figure 139: Psychological status (Beck Anxiety Inventory)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Relaxation techniques Mean	Relaxation techniques SD	Relaxation techniques Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	11.45	10.22	29	11.41	10.06	28	100.0%	0.04 [-5.23, 5.31]
Total (95% CI)			**29**			**28**	**100.0%**	**0.04 [-5.23, 5.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)

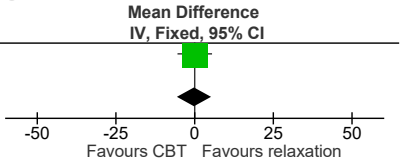

Figure 140: Return to school/work (employment)

Study or Subgroup	CBT Events	CBT Total	Relaxation techniques Events	Relaxation techniques Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jason 2007	18	29	10	29	100.0%	1.80 [1.01, 3.20]
Total (95% CI)		**29**		**29**	**100.0%**	**1.80 [1.01, 3.20]**
Total events	18		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)

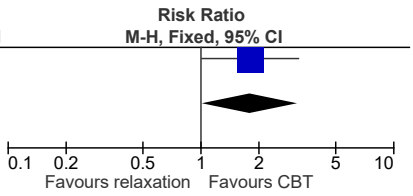

Figure 141: Exercise performance measure (6 minute walk)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Relaxation techniques Mean	Relaxation techniques SD	Relaxation techniques Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	1,542.6	634.11	29	1,378.4	208.92	29	100.0%	164.20 [-78.79, 407.19]
Total (95% CI)			**29**			**29**	**100.0%**	**164.20 [-78.79, 407.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)

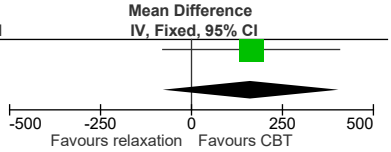

Figure 142: Pain (Brief Pain Inventory - severity)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Relaxation techniques Mean	Relaxation techniques SD	Relaxation techniques Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	3.56	2.57	29	3.63	2.72	29	100.0%	-0.07 [-1.43, 1.29]
Total (95% CI)			**29**			**29**	**100.0%**	**-0.07 [-1.43, 1.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

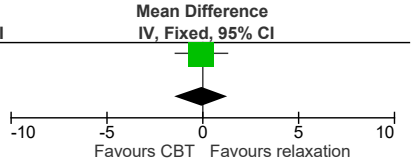

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Figure 143: Pain (Brief Pain Inventory - interference)

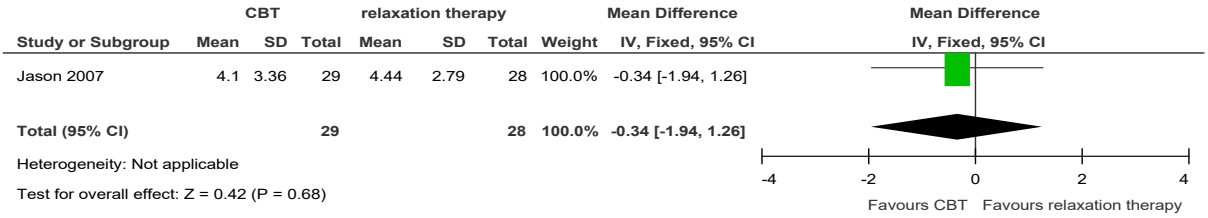
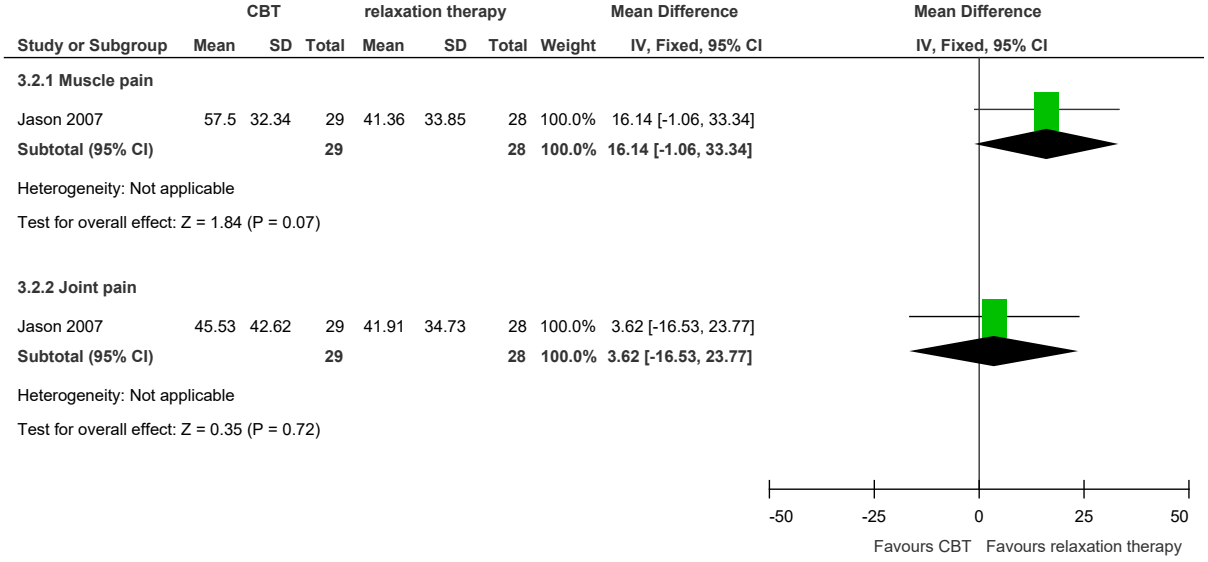


Figure 144: Pain (Muscle pain & joint pain numeric rating scale)



E.2.12 Individual face-to-face cognitive behavioural therapy versus cognitive therapy: adults, moderate severity

Figure 145: Quality of life (Quality of Life Scale)

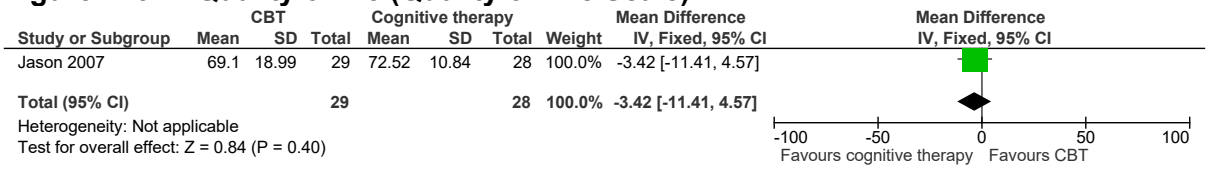


Figure 146: General symptom scales (self-rated global impression of change improved/much improved/very much improved)

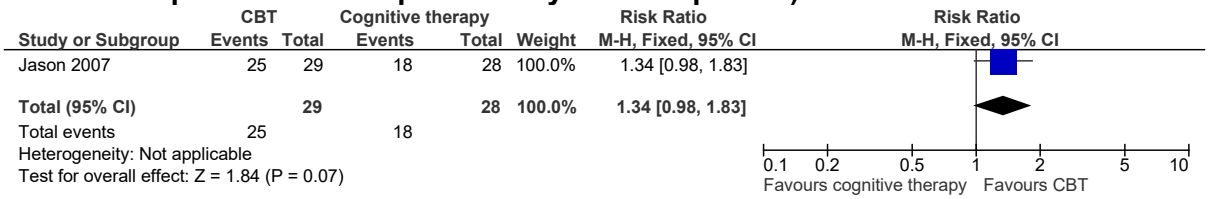


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Figure 147: Fatigue (Fatigue Severity Scale)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Cognitive therapy Mean	Cognitive therapy SD	Cognitive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	5.37	1.19	29	5.87	1.01	28	100.0%	-0.50 [-1.07, 0.07]
Total (95% CI)			**29**			**28**	**100.0%**	**-0.50 [-1.07, 0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)

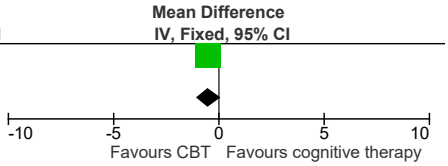

Figure 148: Physical functioning (SF36 physical functioning)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Cognitive therapy Mean	Cognitive therapy SD	Cognitive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	58.64	30.44	29	61.09	23.74	28	100.0%	-2.45 [-16.59, 11.69]
Total (95% CI)			**29**			**28**	**100.0%**	**-2.45 [-16.59, 11.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)

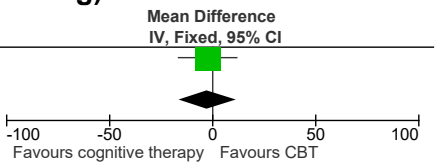

Figure 149: Psychological status (Beck depression inventory)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Cognitive therapy Mean	Cognitive therapy SD	Cognitive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	13.95	13.08	29	11.86	7.36	28	100.0%	2.09 [-3.40, 7.58]
Total (95% CI)			**29**			**28**	**100.0%**	**2.09 [-3.40, 7.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)

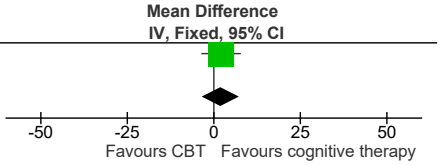

Figure 150: Psychological status (Beck Anxiety Inventory)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Cognitive therapy Mean	Cognitive therapy SD	Cognitive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	11.45	10.22	29	8.96	6.87	28	100.0%	2.49 [-2.02, 7.00]
Total (95% CI)			**29**			**28**	**100.0%**	**2.49 [-2.02, 7.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

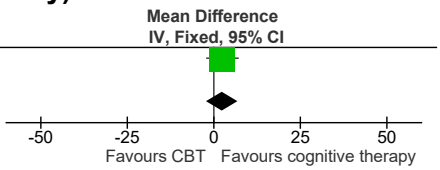

Figure 151: Return to school/work (employment)

Study or Subgroup	CBT Events	CBT Total	Cognitive therapy Events	Cognitive therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jason 2007	18	29	16	28	100.0%	1.09 [0.71, 1.67]
Total (95% CI)		**29**		**28**	**100.0%**	**1.09 [0.71, 1.67]**
Total events	18		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)

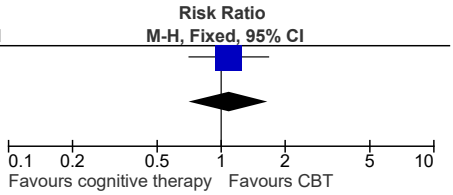

Figure 152: Exercise performance measure (6 minute walk)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Cognitive therapy Mean	Cognitive therapy SD	Cognitive therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	1,542.6	634.11	29	1,513.5	270.95	28	100.0%	29.10 [-222.56, 280.76]
Total (95% CI)			**29**			**28**	**100.0%**	**29.10 [-222.56, 280.76]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

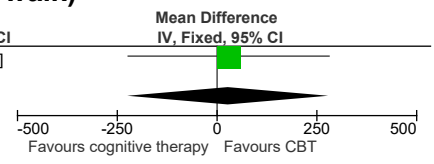

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Figure 153: Pain (Brief Pain Inventory - severity)

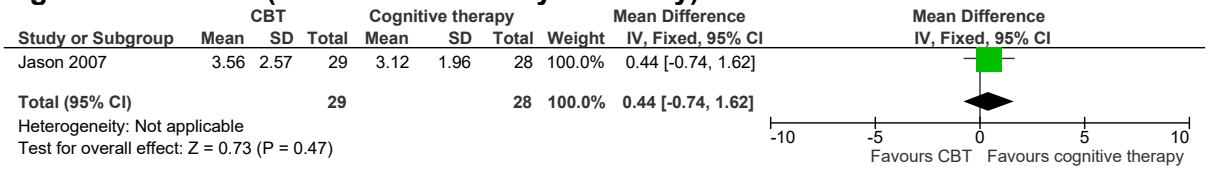


Figure 154: Pain (Brief Pain Inventory - interference)

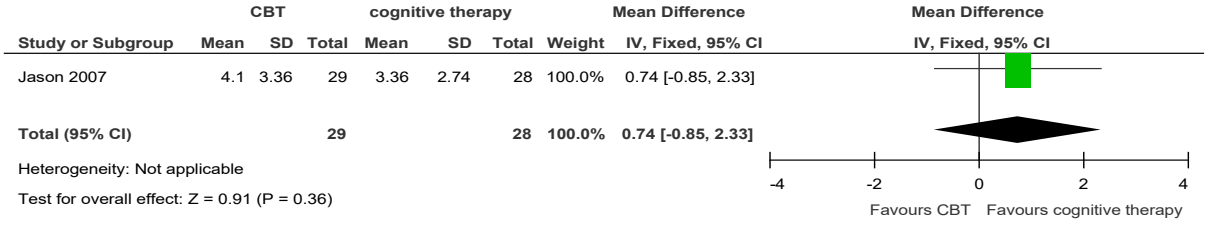
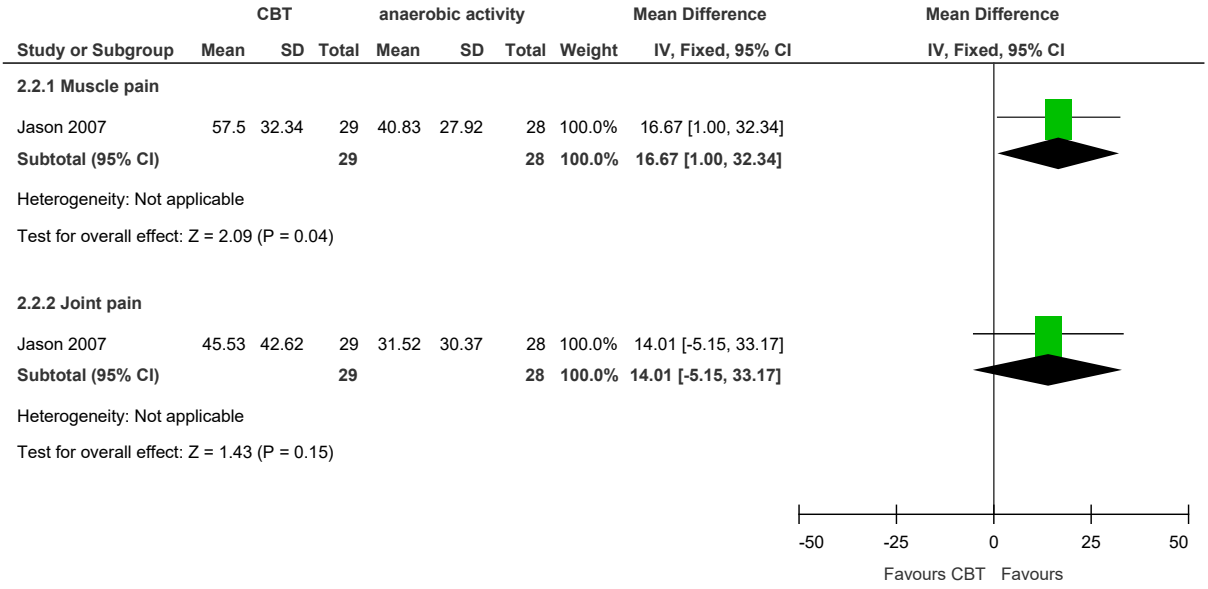


Figure 155: Pain (Muscle pain & joint pain numeric rating scale)



E.2.13 Individual face-to-face cognitive behavioural therapy versus anaerobic activity therapy: adults, moderate severity

Figure 156: Quality of life (Quality of Life Scale)

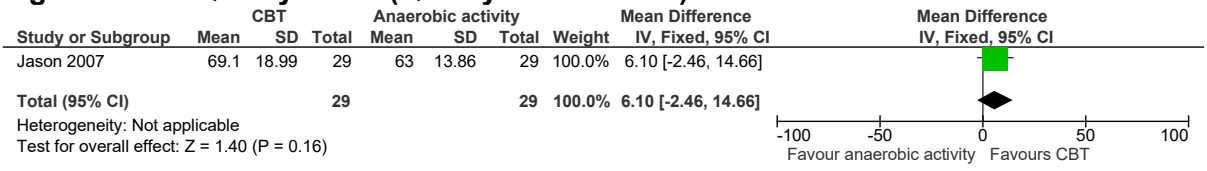


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Figure 157: General symptom scales (self-rated global impression of change improved/much improved/very much improved)

Study or Subgroup	CBT Events	CBT Total	Anaerobic activity Events	Anaerobic activity Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jason 2007	25	29	12	29	100.0%	2.08 [1.32, 3.29]
Total (95% CI)		**29**		**29**	**100.0%**	**2.08 [1.32, 3.29]**
Total events	25		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.15 (P = 0.002)

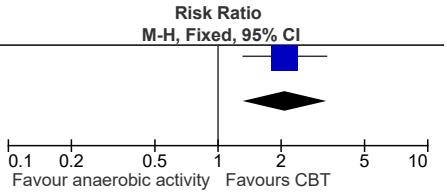

Figure 158: Fatigue (Fatigue Severity Scale)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Anaerobic activity Mean	Anaerobic activity SD	Anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	5.37	1.19	29	5.77	1.43	29	100.0%	-0.40 [-1.08, 0.28]
Total (95% CI)			**29**			**29**	**100.0%**	**-0.40 [-1.08, 0.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)

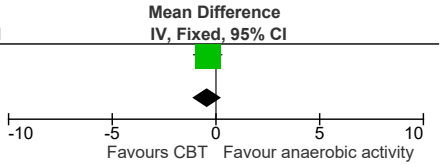

Figure 159: Physical functioning (SF36 physical functioning)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Anaerobic activity Mean	Anaerobic activity SD	Anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	58.64	30.44	29	39.72	27.63	29	100.0%	18.92 [3.96, 33.88]
Total (95% CI)			**29**			**29**	**100.0%**	**18.92 [3.96, 33.88]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.48 (P = 0.01)

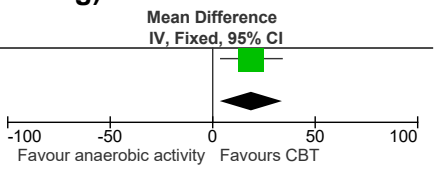

Figure 160: Psychological status (Beck depression inventory)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Anaerobic activity Mean	Anaerobic activity SD	Anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	13.95	13.08	29	16.94	11.82	29	100.0%	-2.99 [-9.41, 3.43]
Total (95% CI)			**29**			**29**	**100.0%**	**-2.99 [-9.41, 3.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)

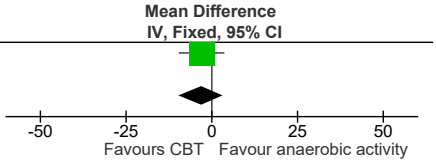

Figure 161: Psychological status (Beck Anxiety Inventory)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Anaerobic activity Mean	Anaerobic activity SD	Anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	11.45	10.22	29	12.11	10.08	29	100.0%	-0.66 [-5.88, 4.56]
Total (95% CI)			**29**			**29**	**100.0%**	**-0.66 [-5.88, 4.56]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

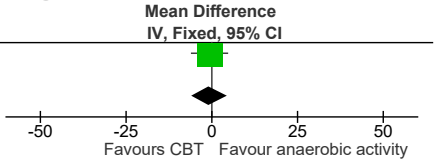

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Figure 162: Return to school/work (employment)

Study or Subgroup	CBT Events	CBT Total	Anaerobic activity Events	Anaerobic activity Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jason 2007	18	29	10	29	100.0%	1.80 [1.01, 3.20]
Total (95% CI)		**29**		**29**	**100.0%**	**1.80 [1.01, 3.20]**
Total events	18		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)

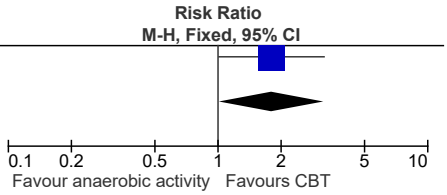

Figure 163: Exercise performance measure (6 minute walk)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Anaerobic activity Mean	Anaerobic activity SD	Anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	1,542.6	634.11	29	1,378.4	208.92	29	100.0%	164.20 [-78.79, 407.19]
Total (95% CI)			**29**			**29**	**100.0%**	**164.20 [-78.79, 407.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)

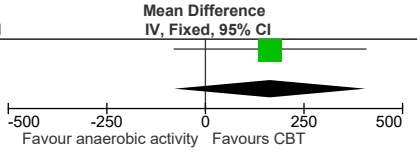

Figure 164: Pain (Brief Pain Inventory - severity)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Anaerobic activity Mean	Anaerobic activity SD	Anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	3.56	2.57	29	3.63	2.72	29	100.0%	-0.07 [-1.43, 1.29]
Total (95% CI)			**29**			**29**	**100.0%**	**-0.07 [-1.43, 1.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

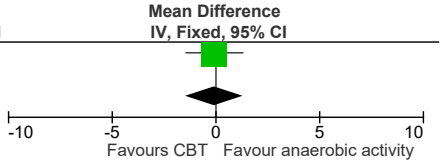

Figure 165: Pain (Brief Pain Inventory - interference)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	anaerobic activity Mean	anaerobic activity SD	anaerobic activity Total	Weight	Mean Difference IV, Fixed, 95% CI
Jason 2007	4.1	3.36	29	3.75	3.14	29	100.0%	0.35 [-1.32, 2.02]
Total (95% CI)			**29**			**29**	**100.0%**	**0.35 [-1.32, 2.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

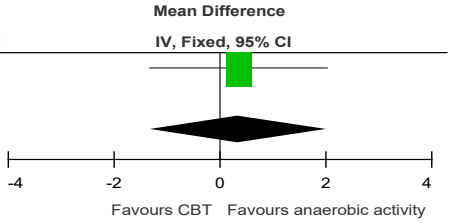

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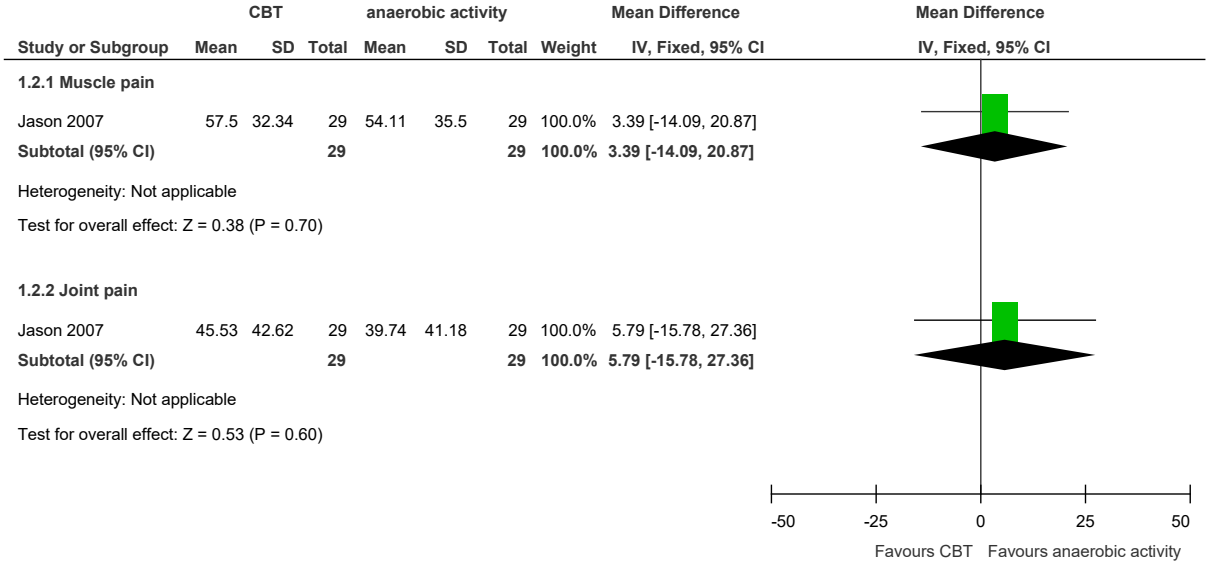
Figure 166: Pain (Muscle pain & joint pain numeric rating scale)



E.2.14 Individual face-to-face cognitive behavioural therapy versus psycho-education/pacing: children and young people, severity mixed or unclear

Figure 167: General symptom scales (Self-reported global improvement - much better or very much better)

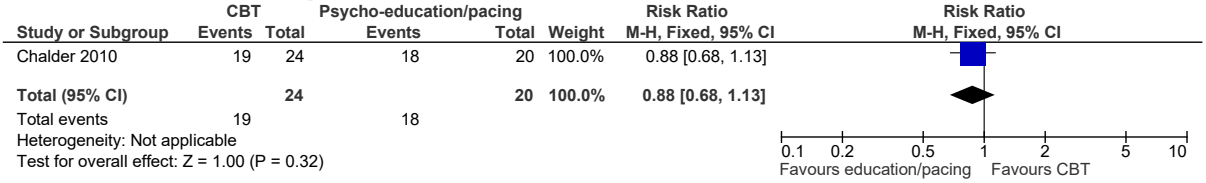


Figure 168: General symptom scales (Strengths and Difficulties Questionnaire)

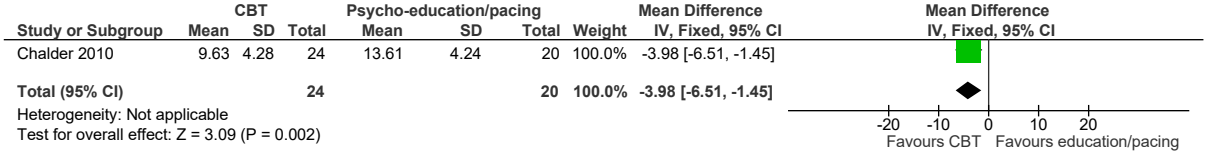


Figure 169: Fatigue/fatigability (Chalder Fatigue Scale)

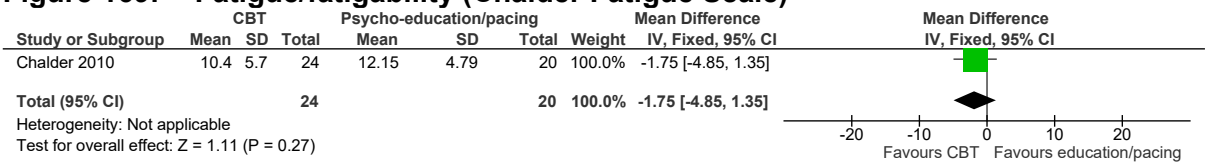


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Figure 170: Physical functioning (SF36 physical functioning)

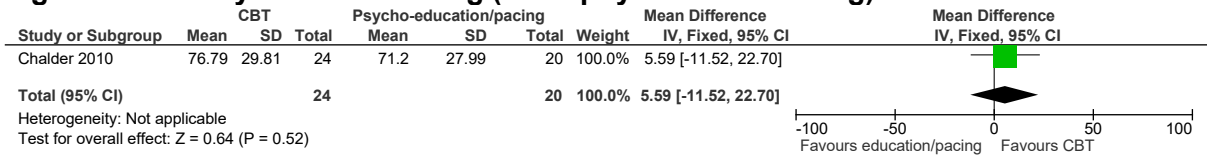


Figure 171: Adverse events (Serious adverse events)

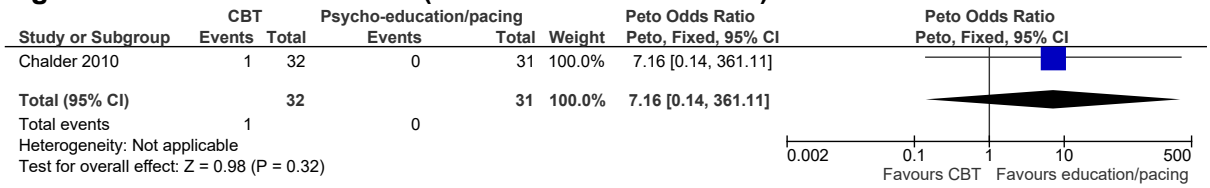


Figure 172: Return to school or work (% school attendance over 2 weeks)

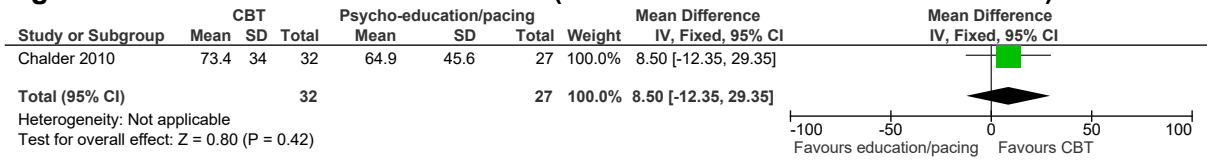
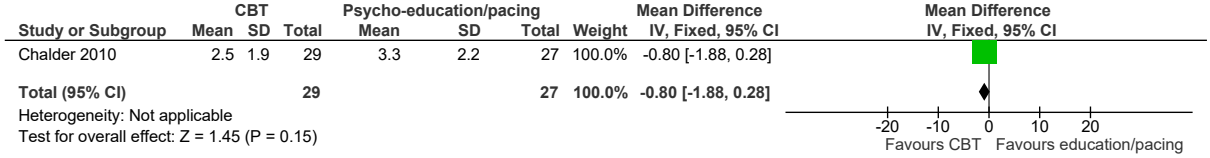


Figure 173: Return to school or work (Work and Social Adjustment Scale)



E.2.15 Individual face-to-face cognitive behavioural therapy versus waiting list: children and young people, severity mixed or unclear

Figure 174: General symptom scales (self-rated improvement recovered or much better)

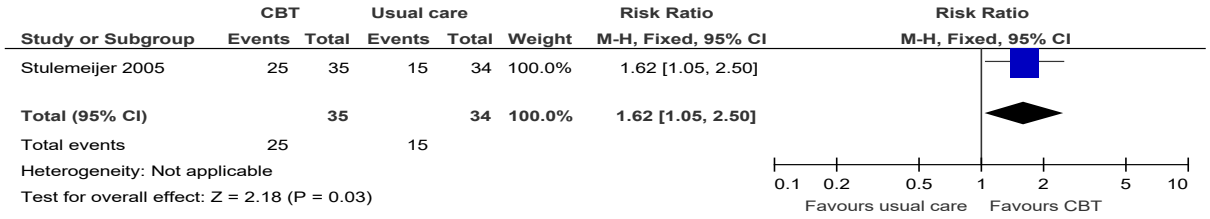


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Figure 175: Fatigue (Checklist Individual Strength - fatigue severity sub scale)

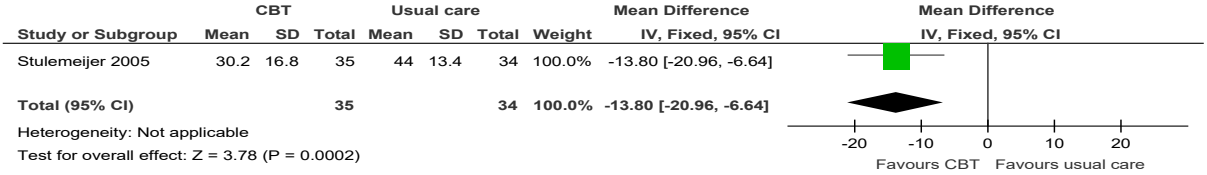

Figure 176: Physical functioning (SF36 physical function)

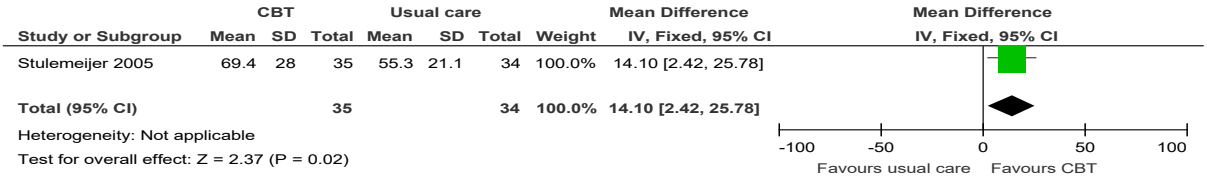

Figure 177: Return to school or work (School attendance (hours attended/total hours))

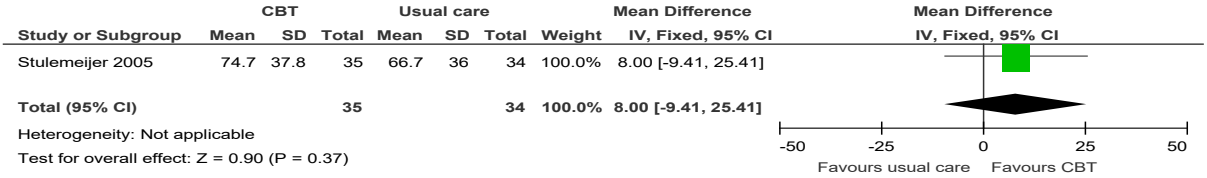

Figure 178: Cognitive function (Checklist individual strength – concentration sub scale)

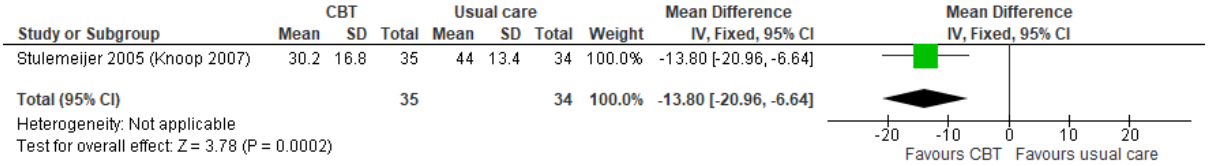

Figure 179: Cognitive function (Reaction time tests – simple and choice)

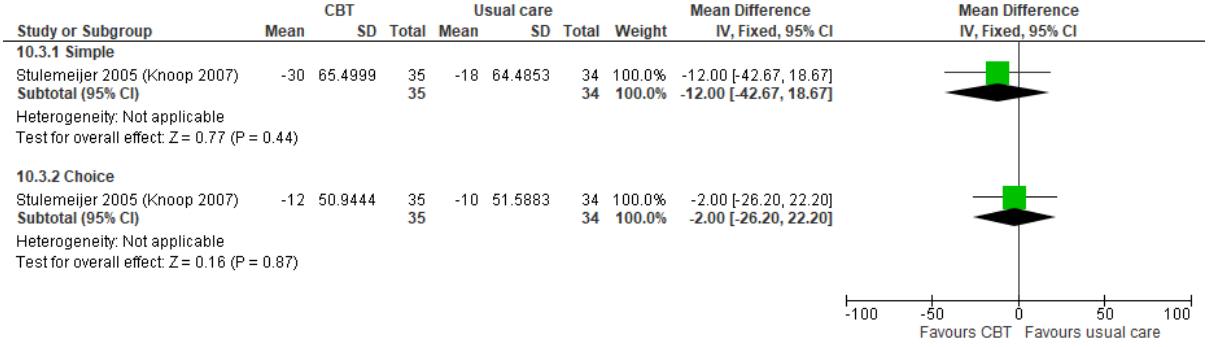

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Figure 180: Pain (Daily pain – 0-4 scale) (change scores)

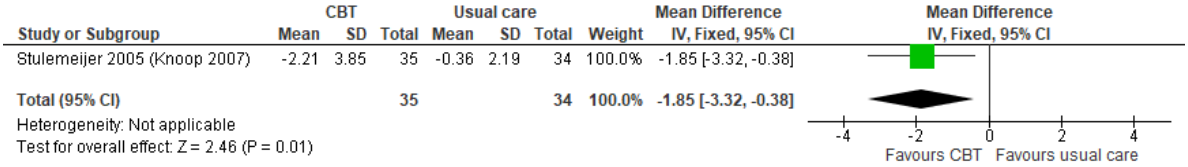
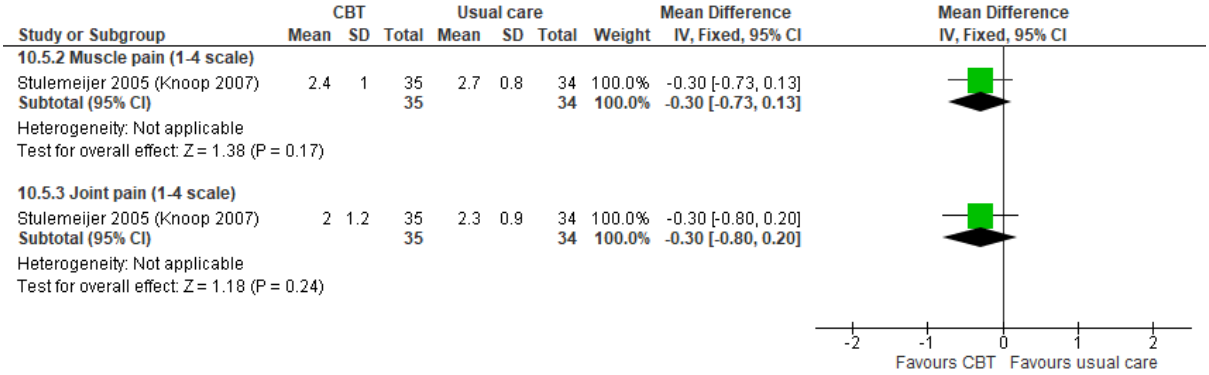


Figure 181: Pain (Muscle pain & joint pain – 1-4 scale)



E.2.16 Web/written cognitive behavioural therapy versus usual care: children and young people, severity mixed or unclear

Figure 182: General symptom scales (Self rated improvement completely recovered or much better)

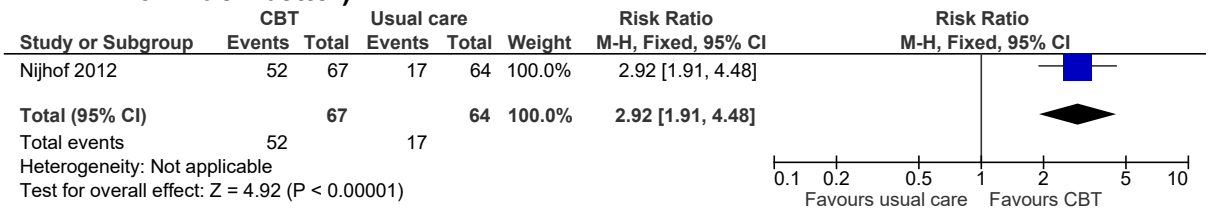


Figure 183: Fatigue (Checklist individual strength-20 – fatigue severity)

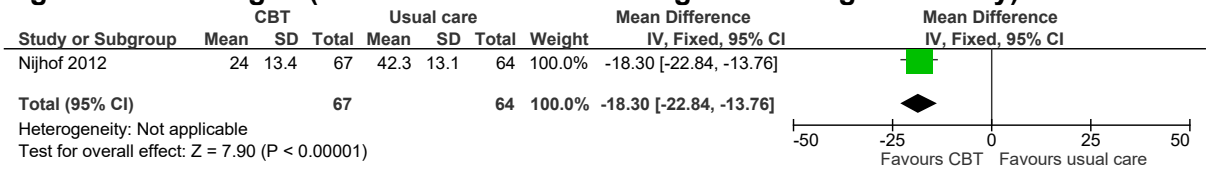


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Figure 184: Physical functioning (Physical functioning (Child health questionnaire)

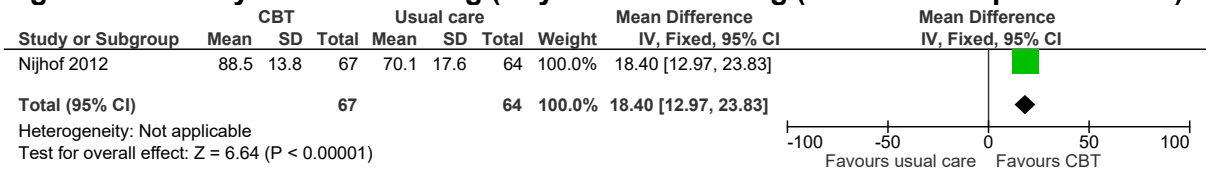


Figure 185: Adverse events (serious adverse events)

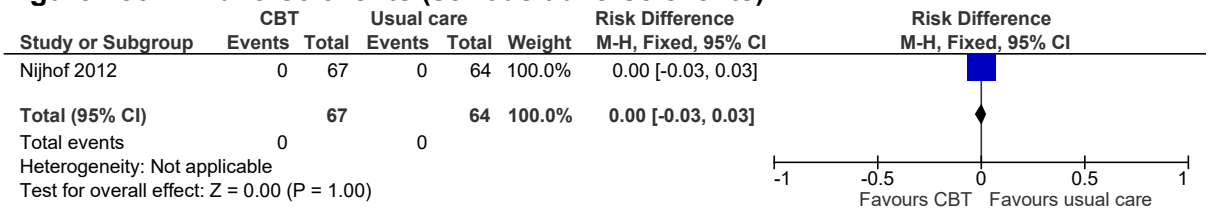
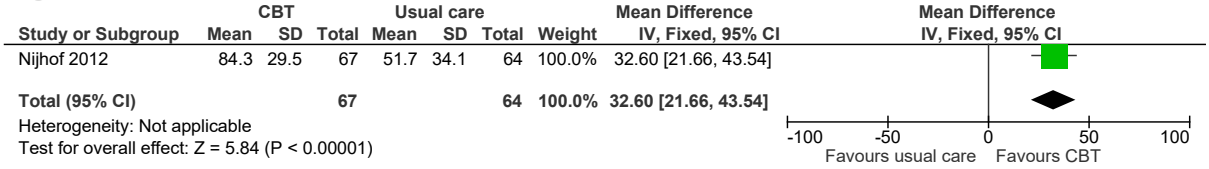


Figure 186: Return to school or work (mean % school attendance)



E.2.17 Individual face-to-face cognitive behavioural therapy + biofeedback versus standard care: children and young people, severity mixed or unclear

Figure 187: Fatigue (Fatigue Assessment Scale %)

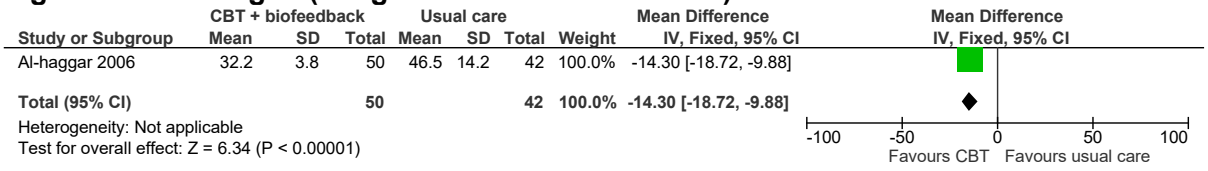
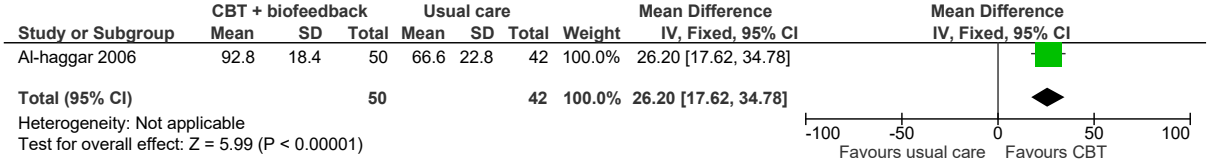


Figure 188: Return to school or work (School attendance hours/month)



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Other psychological interventions

E.2.18 Education and support group versus usual care: adults, severity mixed or unclear

Figure 189: Quality of life (SF36)

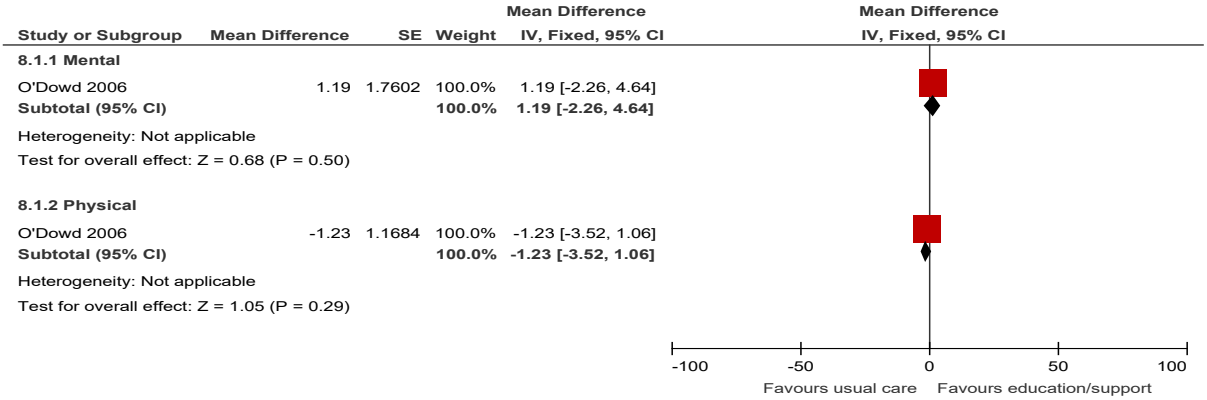

Figure 190: Quality of life (Health status (HUI3))

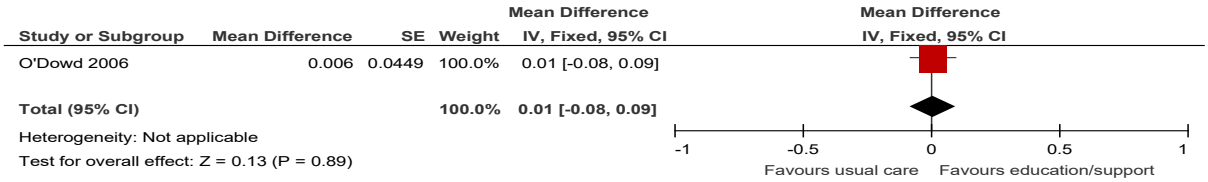

Figure 191: Fatigue/fatigability (Chalder fatigue questionnaire)

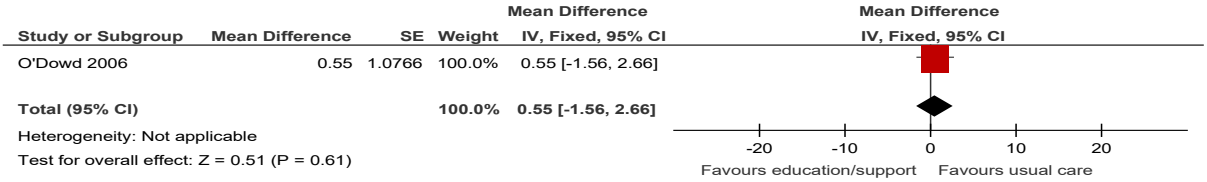

Figure 192: Cognitive function (total words recalled)

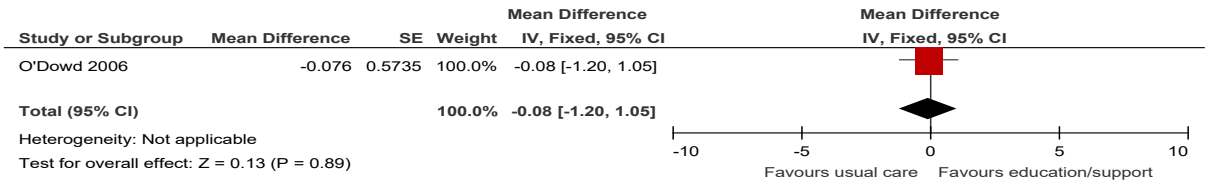

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Figure 193: Cognitive function (correct words)

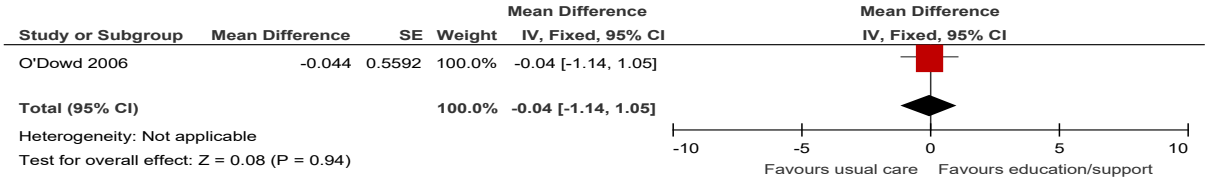

Figure 194: Cognitive function (reaction time)

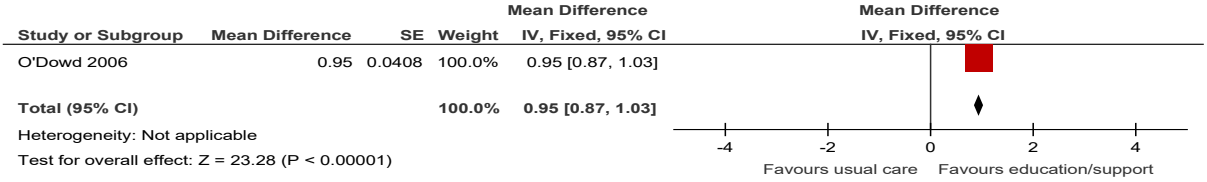

Figure 195: Psychological status (HADS anxiety)

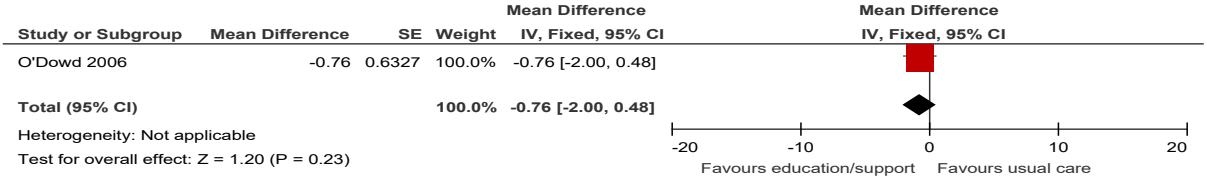

Figure 196: Psychological status (HADS depression)

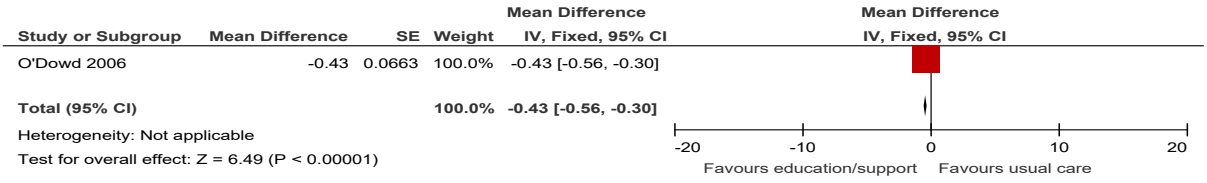

Figure 197: Psychological status (General health questionnaire)

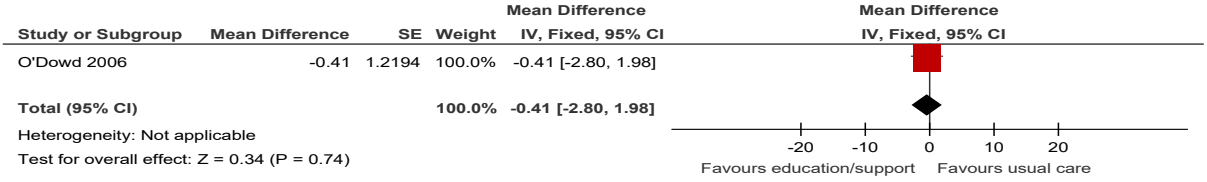

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Figure 198: Exercise performance measure (normal walking speed)

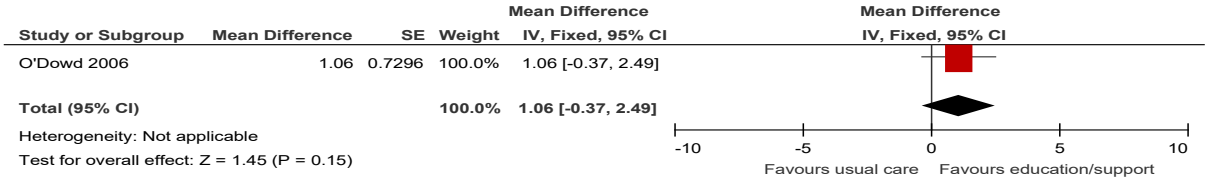


Figure 199: Exercise performance measure (shuttles walked)

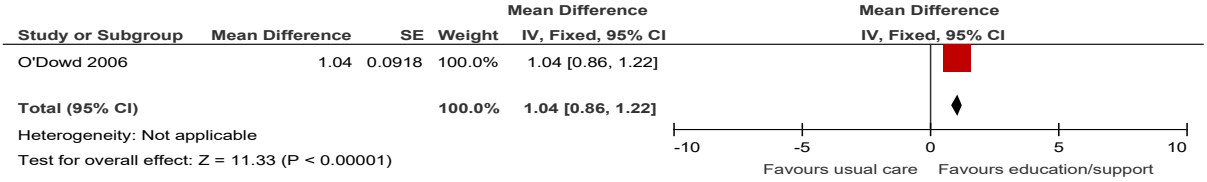
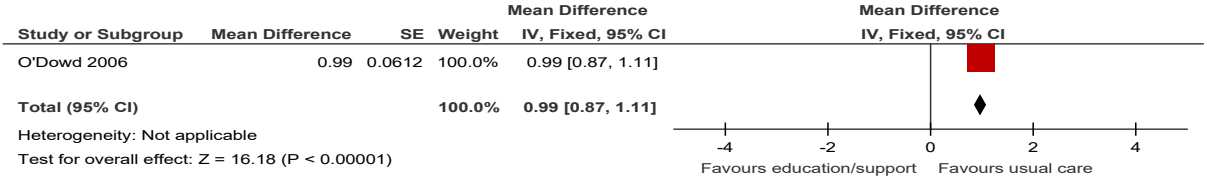


Figure 200: Exercise performance measure (perceived fatigue- modified Borg scale)



E.2.19 Cognitive therapy versus relaxation: adults, moderate severity

Figure 201: Quality of life (Quality of Life Scale)

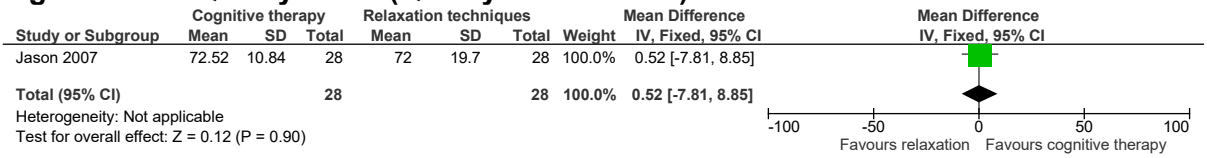


Figure 202: General symptom scales (self-rated global impression of change improved/much improved/very much improved)

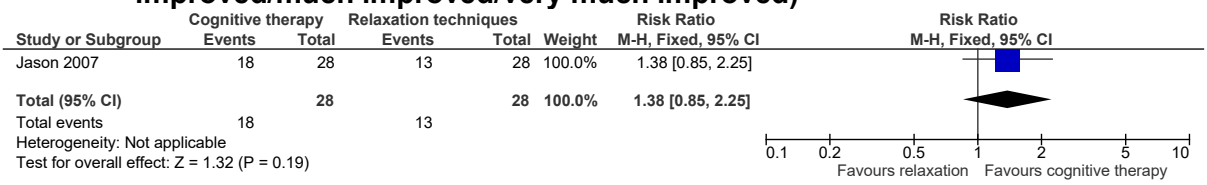


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Figure 203: Fatigue (Fatigue Severity Scale)

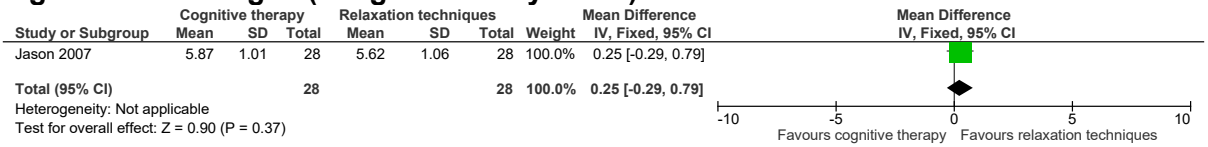

Figure 204: Physical functioning (SF36 physical functioning)

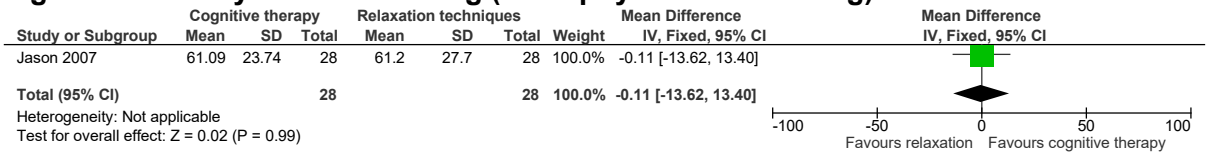

Figure 205: Psychological status (Beck depression inventory)

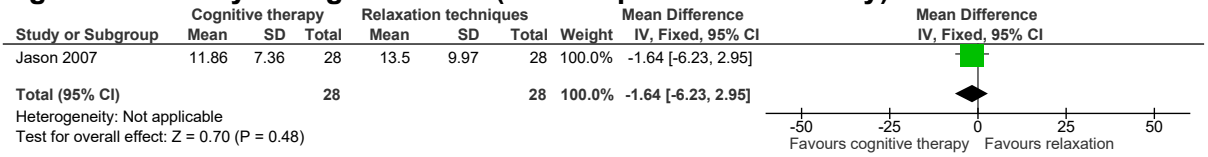

Figure 206: Psychological status (Beck Anxiety Inventory)

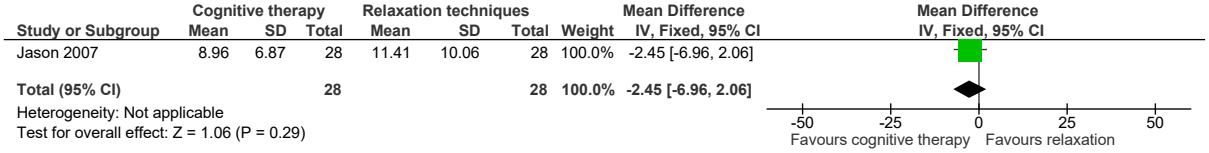

Figure 207: Return to school/work (employment)

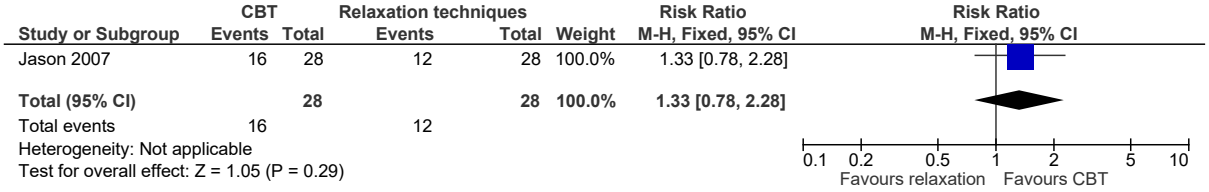

Figure 208: Exercise performance measure (6 minute walk)

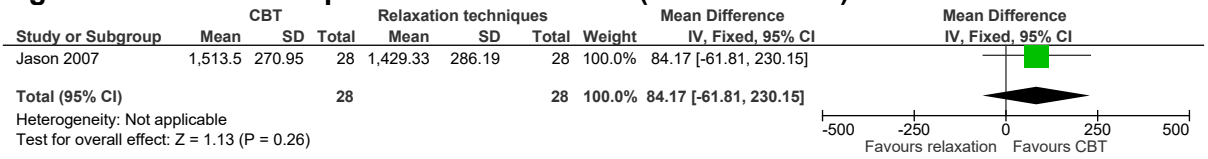

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Figure 209: Pain (Brief Pain Inventory - severity)

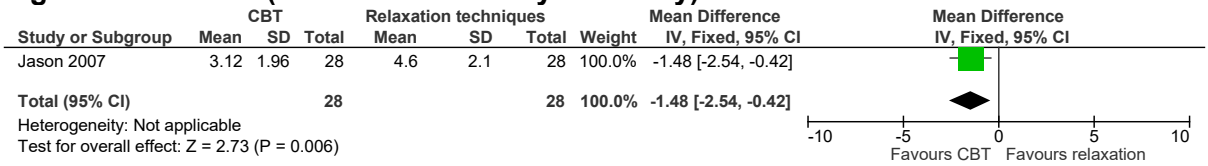


Figure 210: Pain (Brief Pain Inventory - interference)

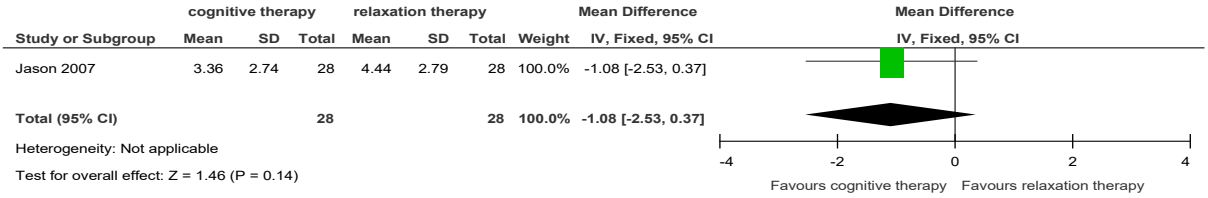
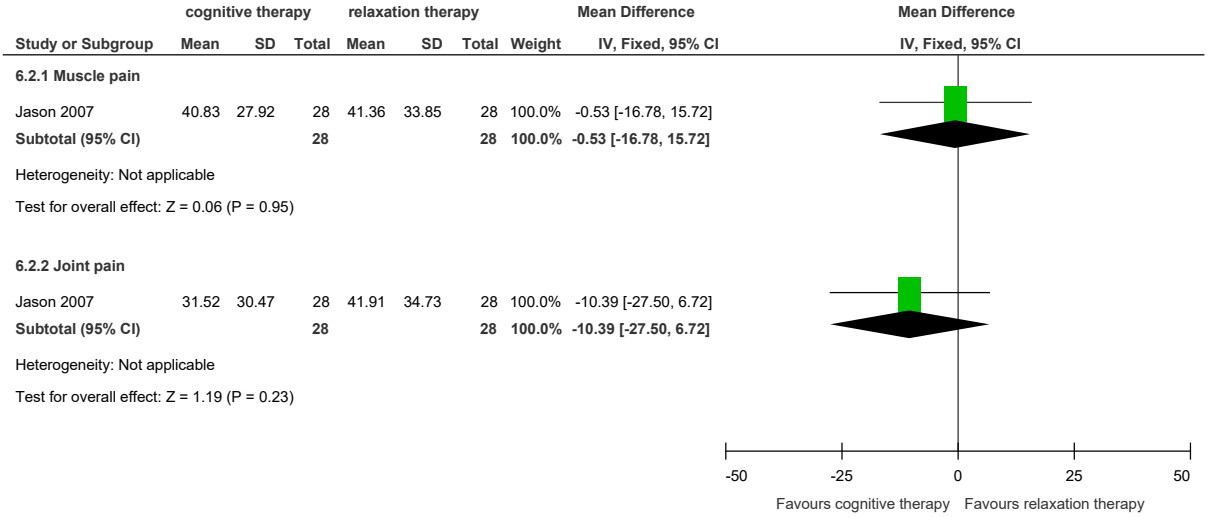


Figure 211: Pain (Muscle pain & joint pain numeric rating scale)



E.2.20 Buddy/mentor programme versus Wait-list: adults, severity mixed or unclear

Figure 212: Quality of Life (Quality of Life Index)

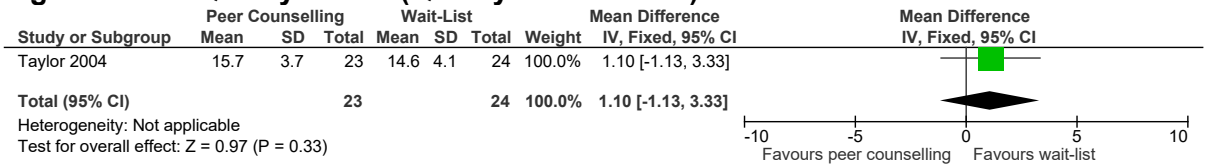


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Figure 213: General Symptom Scales (Chronic Fatigue Syndrome Symptom Rating Form)

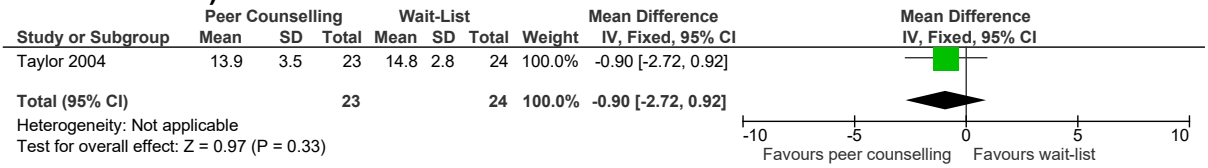


Figure 214: Fatigue (Fatigue Severity Scale)

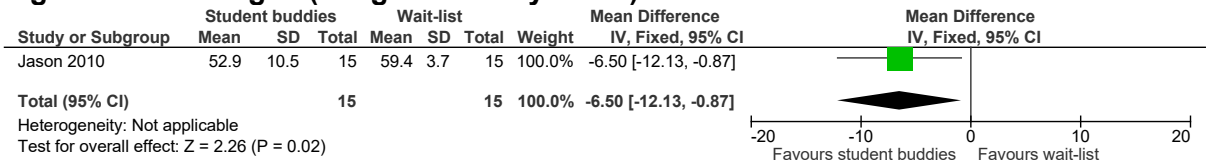


Figure 215: Physical Functioning (SF36 Physical Functioning)

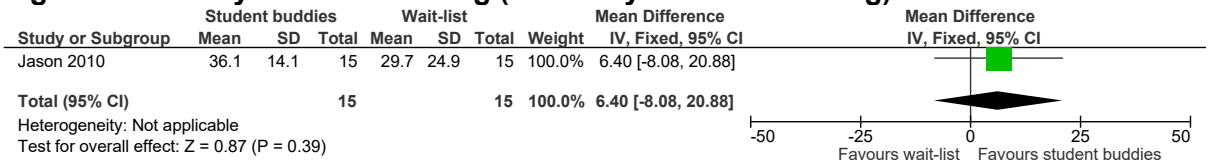


Figure 216: Psychological Status (Perceived Stress Scale)

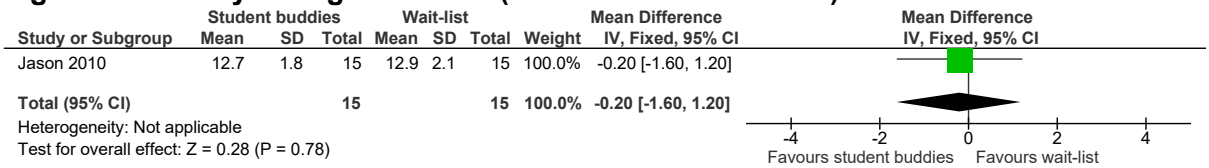
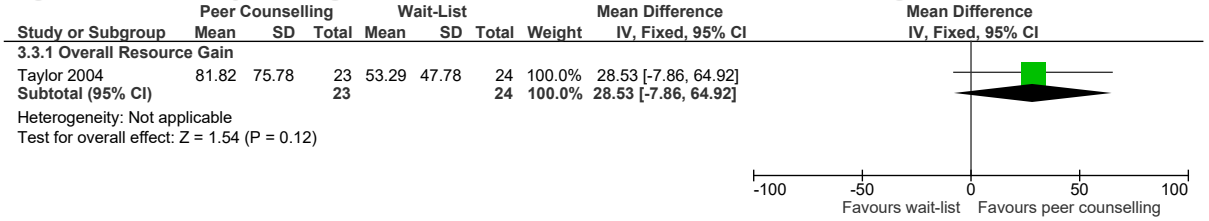
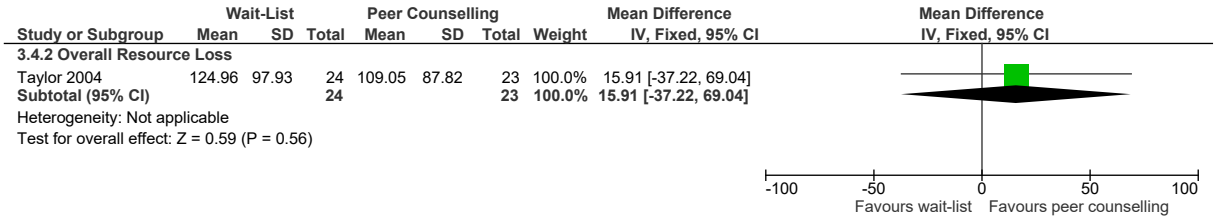


Figure 217: Psychological Status (CORE-E – overall resource gain and loss)





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E.2.21 Pragmatic rehabilitation versus Supportive listening: adults, severity mixed or unclear

Figure 218: Fatigue (Chalder Fatigue Scale)

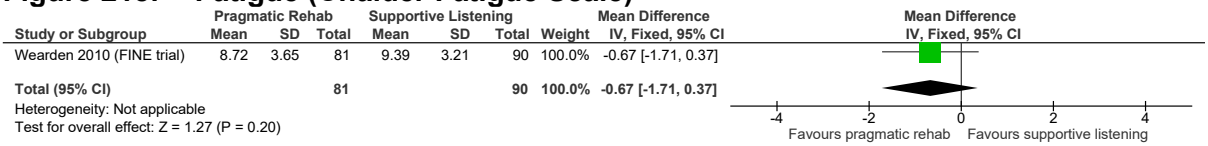


Figure 219: Physical Functioning (SF36 Physical Functioning)

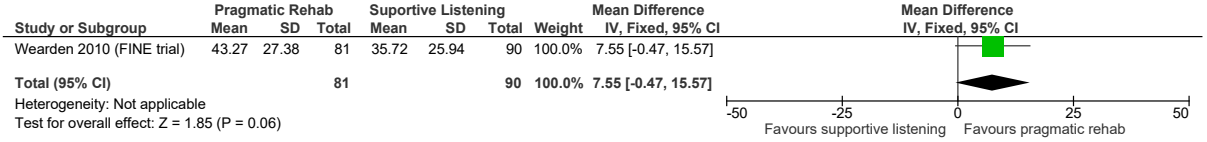


Figure 220: Psychological Status (Hospital Anxiety and Depression Scale)

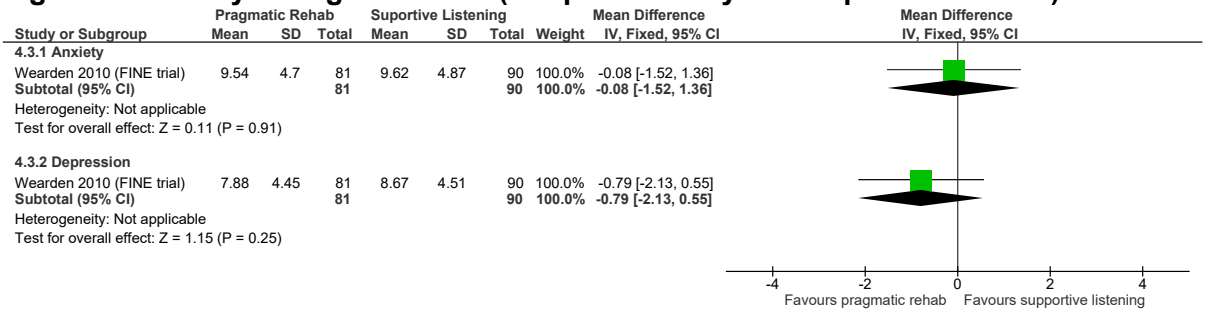
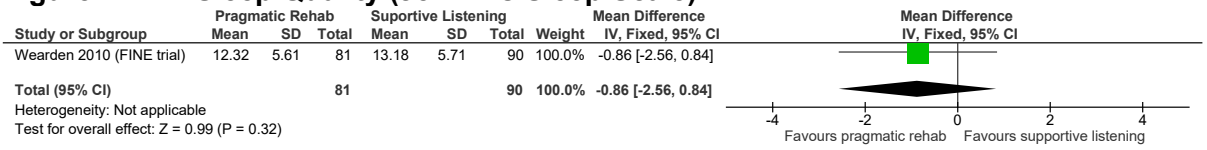


Figure 221: Sleep Quality (Jenkin's Sleep Scale)



E.2.22 Pragmatic rehabilitation versus Usual care: adults, severity mixed or unclear

Figure 222: Fatigue (Chalder Fatigue Scale)

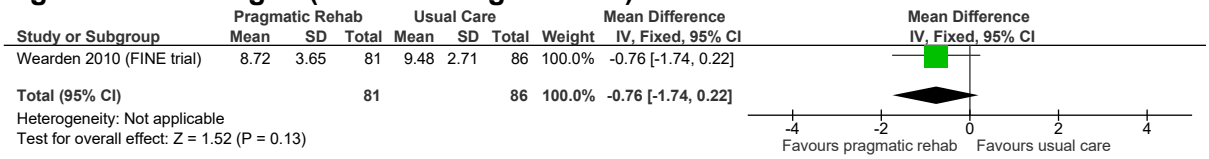


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Figure 223: Physical Functioning (SF36 Physical Functioning)

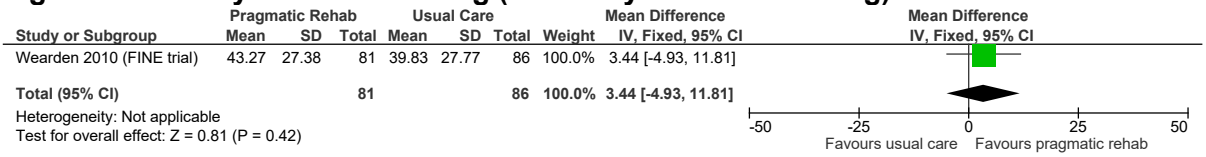


Figure 224: Psychological Status (Hospital Anxiety and Depression Scale)

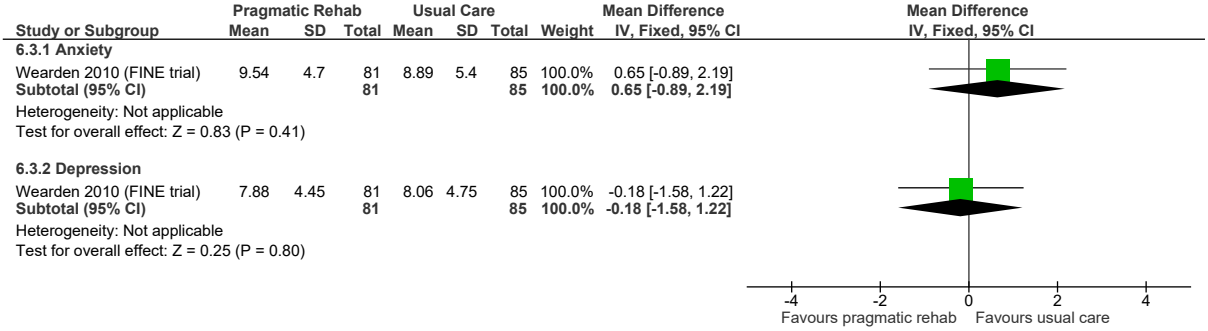


Figure 225: Sleep Quality (Jenkin's Sleep Scale)

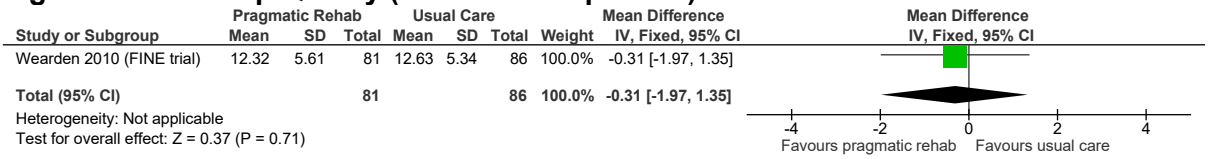
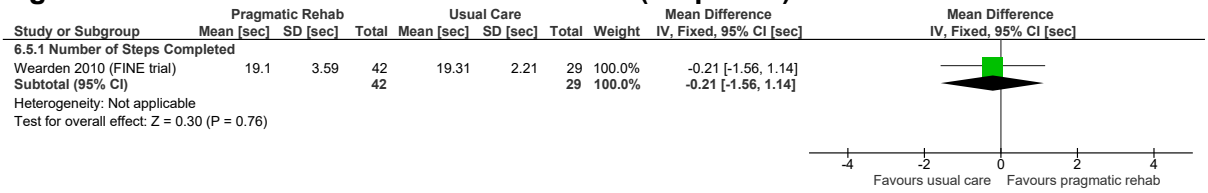


Figure 226: Exercise Performance Measure (Step-Test)



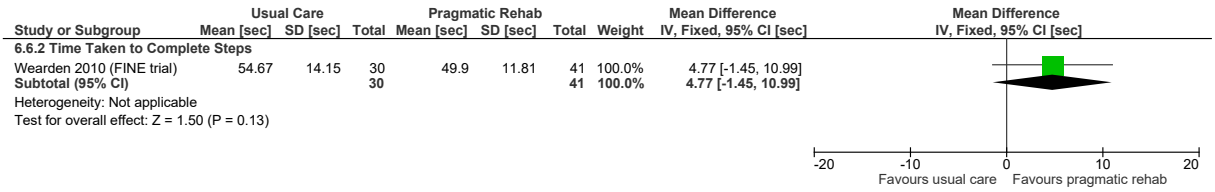


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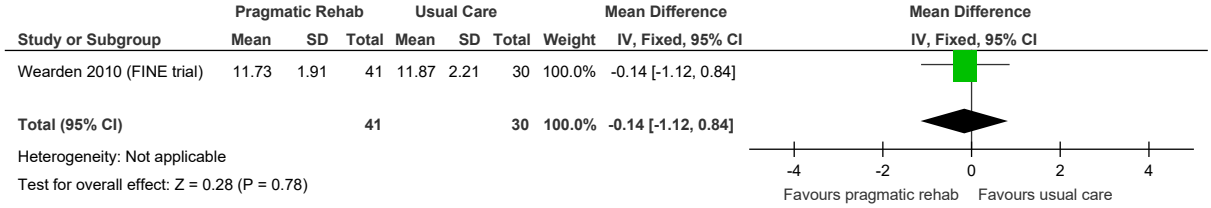
Figure 227: Exercise Performance Measure (Borg Rating of Perceived Exertion)



E.2.23 Supportive Listening versus Usual care: adults, severity mixed or unclear

Figure 228: Fatigue (Chalder Fatigue Scale)

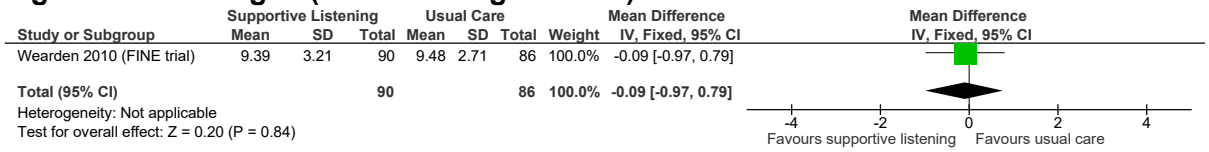


Figure 229: Physical Functioning (SF36 Physical Functioning)

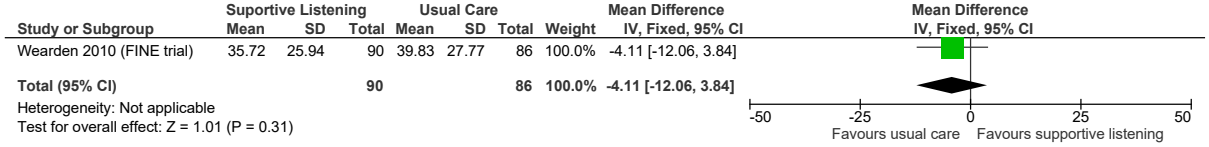


Figure 230: Psychological Status (Hospital Anxiety and Depression Scale)

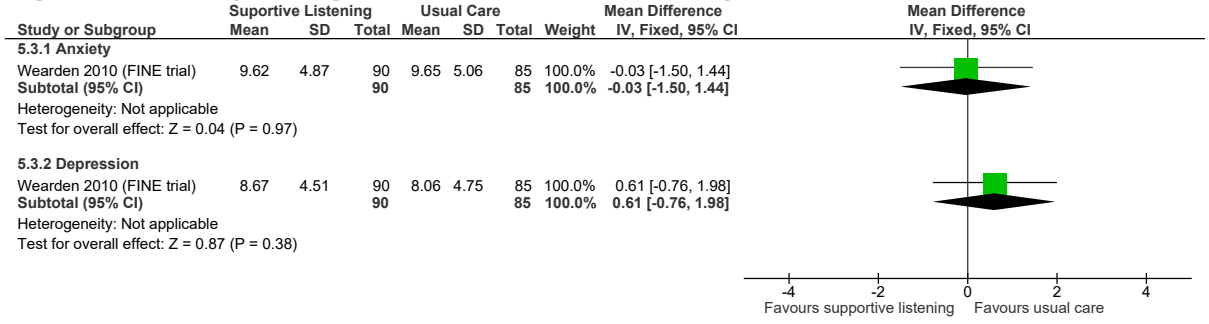
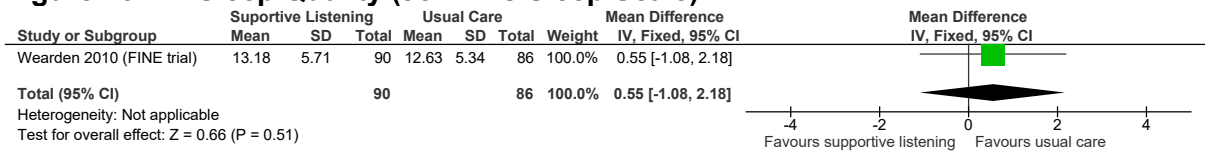


Figure 231: Sleep Quality (Jenkin's Sleep Scale)



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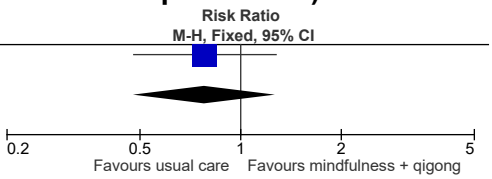
E.2.24 Mindfulness and medical Qigong versus Usual care: adults, severity mixed or unclear

Figure 232: Quality of Life (SF36 Health Transition Score - Improvement)

Study or Subgroup	Mindfulness + Qigong Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Collinge 1998	13	28	19	32	100.0%	0.78 [0.48, 1.28]
Total (95% CI)		**28**		**32**	**100.0%**	**0.78 [0.48, 1.28]**
Total events	13		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



E.2.25 Mindfulness based cognitive therapy versus Wait-list: adults, severity mixed or unclear

Figure 233: Fatigue (Chalder Fatigue Scale, 11-item and 14-item)

Study or Subgroup	Mindfulness Mean	SD	Total	Wait-List Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Rimes 2013	21.3	6.2	15	25	6.1	19	65.5%	-0.59 [-1.28, 0.11]
Surawy 2005	18.56	8.13	9	20.38	8.26	8	34.5%	-0.21 [-1.17, 0.74]
Total (95% CI)			**24**			**27**	**100.0%**	**-0.46 [-1.02, 0.10]**

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)

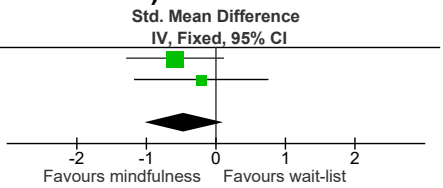


Figure 234: Physical Functioning (SF36 Physical Functioning)

Study or Subgroup	Mindfulness Mean	SD	Total	Wait-List Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Rimes 2013	65.6	26.3	16	55.9	23.3	19	63.8%	9.70 [-6.91, 26.31]
Surawy 2005	40	16.78	9	36.5	27.61	8	36.2%	3.50 [-18.55, 25.55]
Total (95% CI)			**25**			**27**	**100.0%**	**7.46 [-5.81, 20.72]**

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)

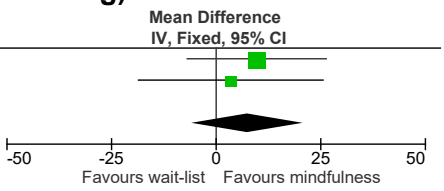


Figure 235: Psychological Status (Hospital Anxiety and Depression Scale)

Study or Subgroup	Mindfulness Mean	SD	Total	Wait-List Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
8.3.1 Anxiety								
Rimes 2013	7.8	3.6	16	8.9	5.2	19	61.7%	-1.10 [-4.03, 1.83]
Surawy 2005	8.22	2.99	9	8.63	4.57	8	38.3%	-0.41 [-4.13, 3.31]
Subtotal (95% CI)			**25**			**27**	**100.0%**	**-0.84 [-3.14, 1.47]**

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)

8.3.2 Depression								
Rimes 2013	5.6	2.9	16	7.7	4.6	19	58.0%	-2.10 [-4.61, 0.41]
Surawy 2005	8.33	1.66	9	9.5	3.96	8	42.0%	-1.17 [-4.12, 1.78]
Subtotal (95% CI)			**25**			**27**	**100.0%**	**-1.71 [-3.62, 0.20]**

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)

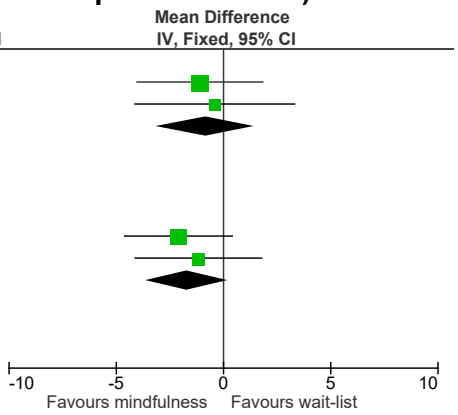


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Figure 236: Return to School or Work (Work and Social Adjustment Scale)

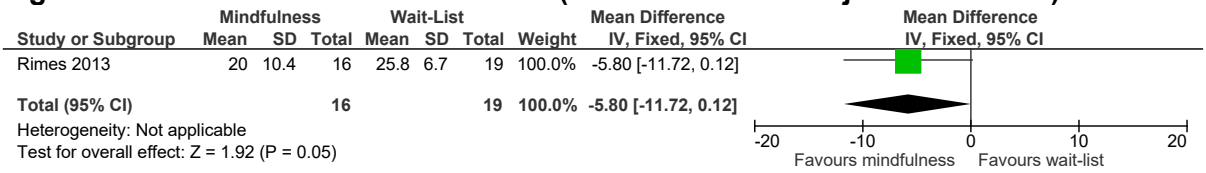
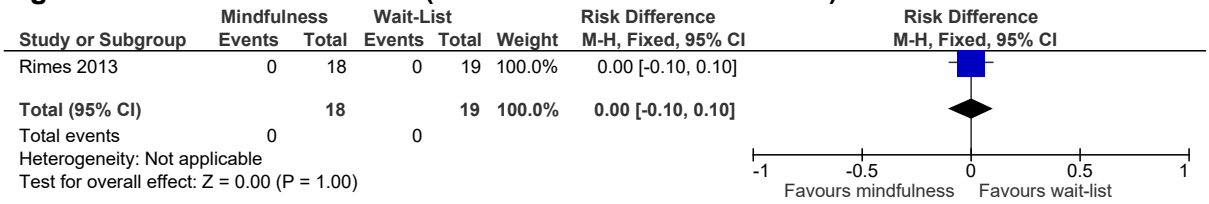


Figure 237: Adverse Events (Substantive Adverse Events)



E.2.26 Focused group therapy versus Wait-list: adults, severity mixed or unclear

Figure 238: Quality of Life (Gothenburg Quality of Life Scale)

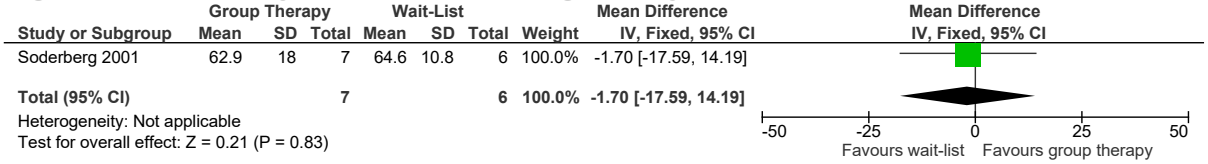
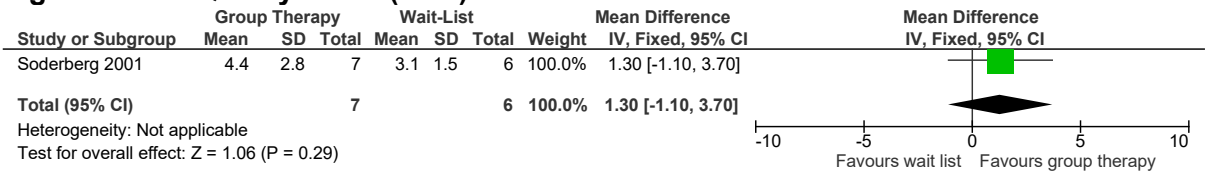


Figure 239: Quality of life (VAS)



E.2.27 The Lightning Process and Specialist Medical Care versus Specialist Medical Care: children and young people, moderate

Figure 240: Fatigue (Chalder Fatigue Scale)

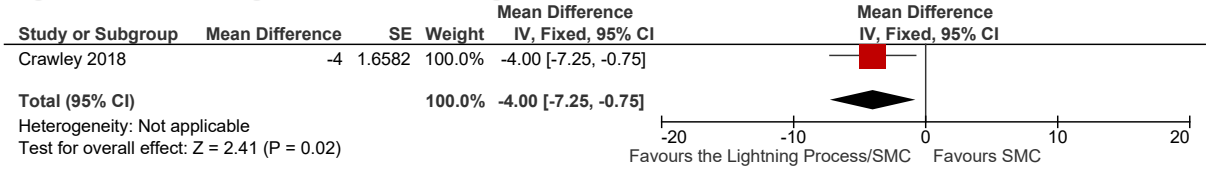


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Figure 241: Physical Functioning (SF36 Physical Functioning)

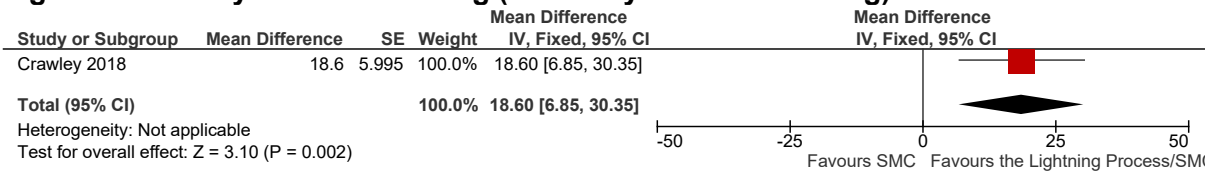

Figure 242: Psychological Status (Spence Children's Anxiety Scale)

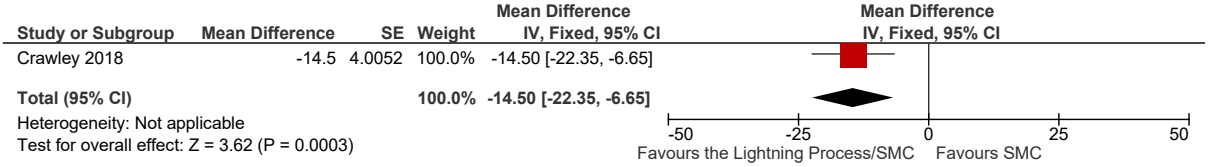

Figure 243: Psychological Status (Hospital Anxiety and Depression Scale)

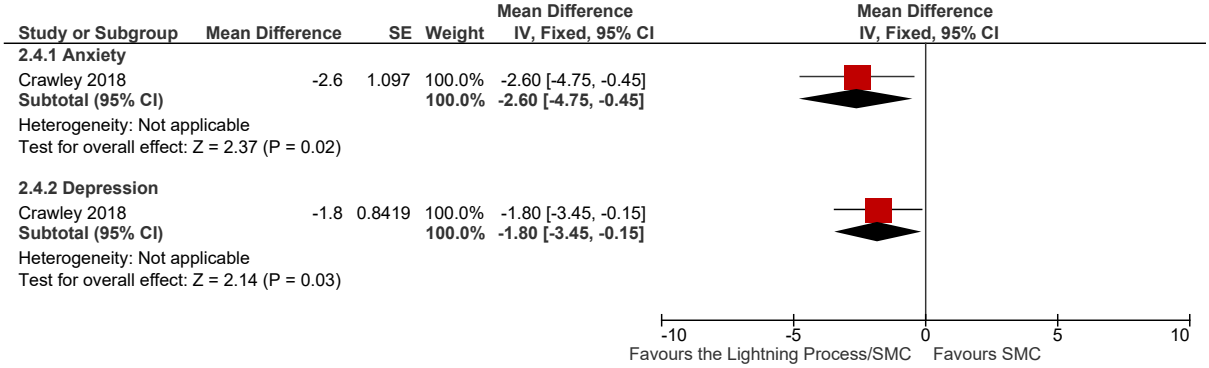

Figure 244: Pain (Visual Analogue Scale)

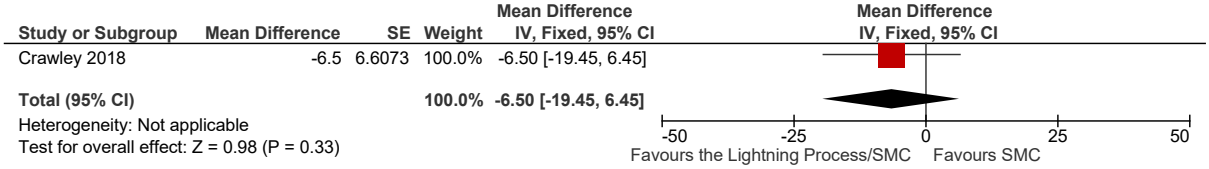

Figure 245: Return to School or Work (School/college attendance in the previous week)

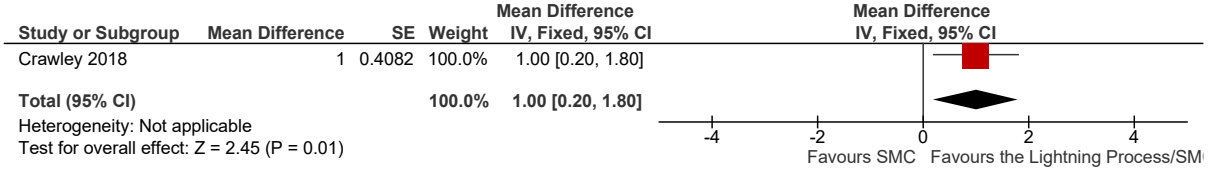

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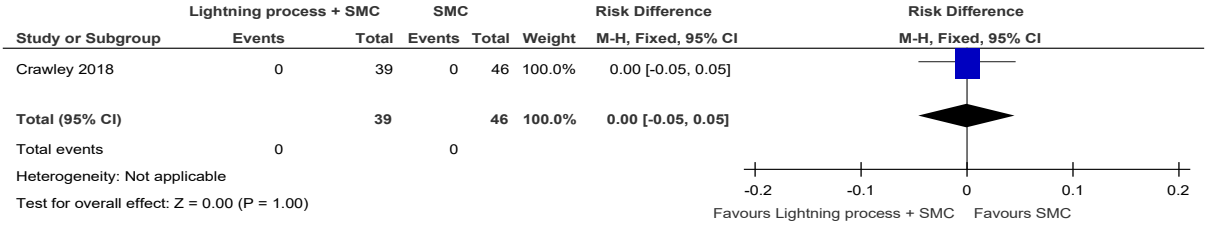
Figure 246: Adverse Events (Serious adverse events attributable to study interventions)



E.3 Exercise interventions

E.3.1 Graded exercise therapy versus standard care: adults, severity mixed or unclear

Figure 247: Quality of life (EQ5D)

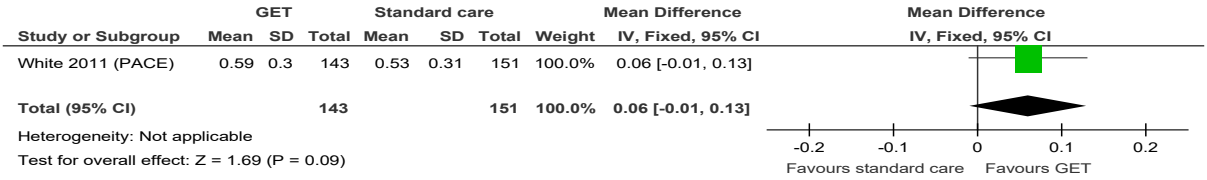


Figure 248: General symptom scales (patient reported global impression of change in CFS positive/much/very much better) (overall and PEM subgroup results)

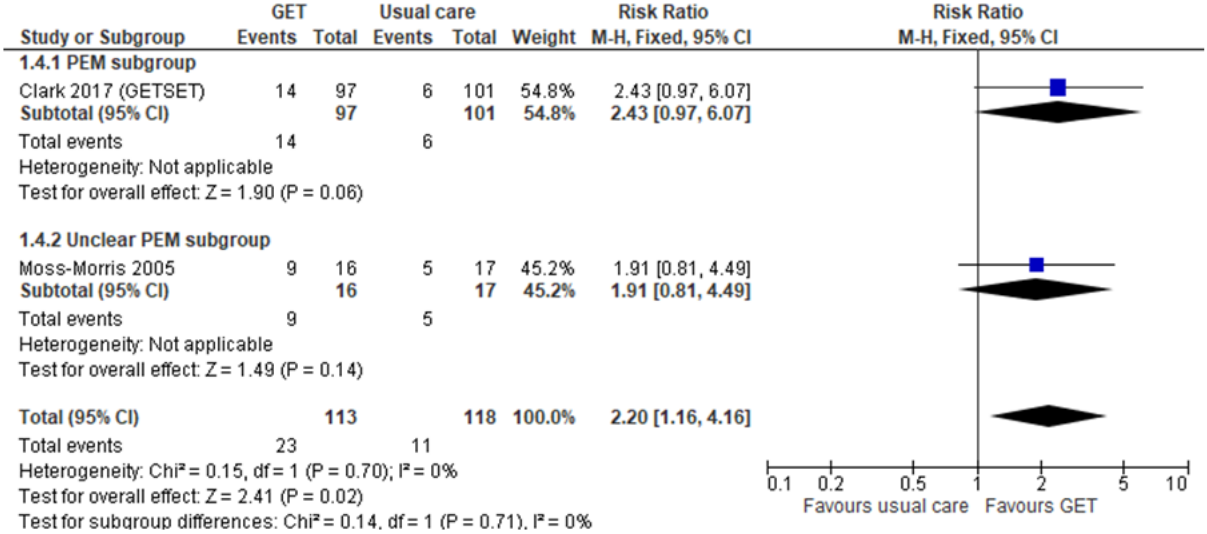


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Figure 249: General symptom scales (clinical global impression scale of change in overall health positive vs. negative/minimal) @ 12 weeks

Figure 250: General symptom scales (clinical global impression scale of change in overall health positive vs. negative/minimal) @ 134 weeks

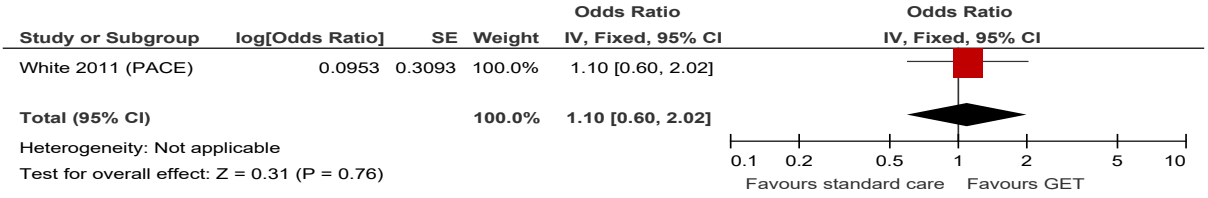
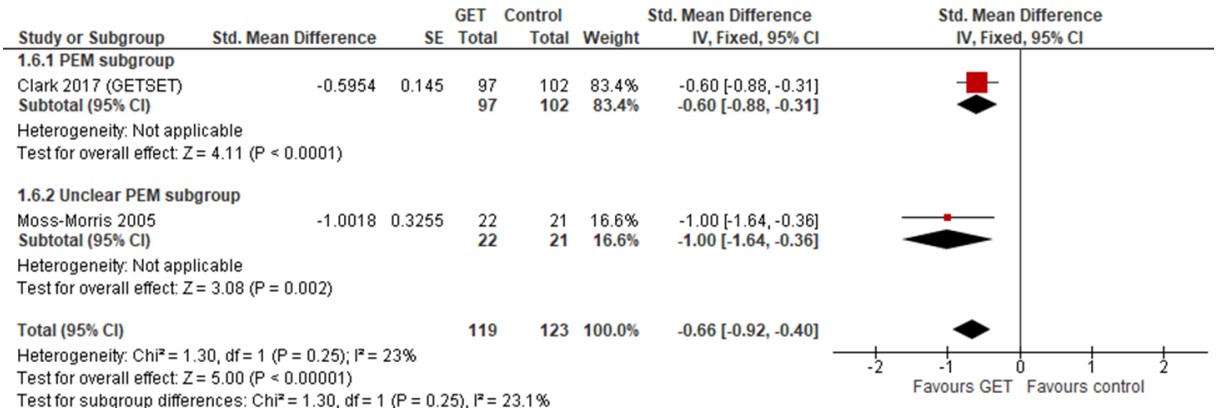


Figure 251: Fatigue/fatigability (Chalder fatigue questionnaire) (overall and PEM subgroup results; SMD for combined scales and MD for individual scales)

Combined scales (SMD)



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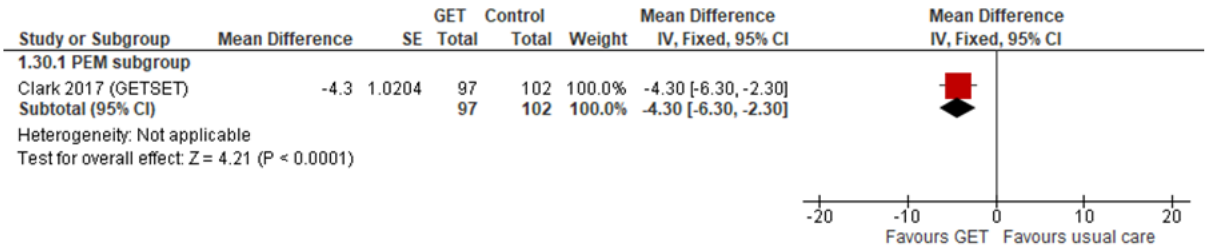
0-33 scale (MD)



0-42 scale (MD)

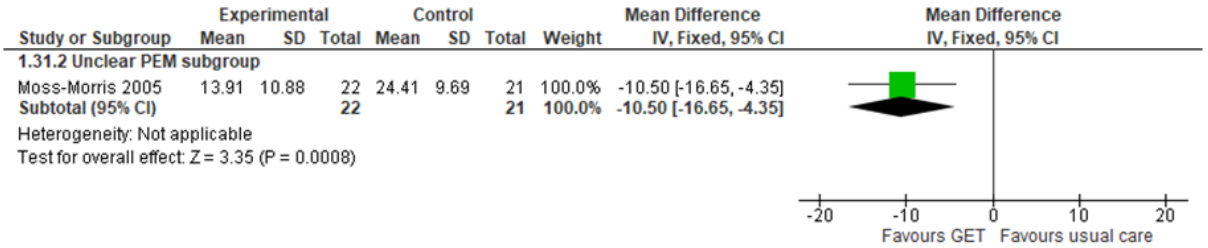


Figure 252: Fatigue/fatigability (Chalder fatigue questionnaire total) at 134 weeks

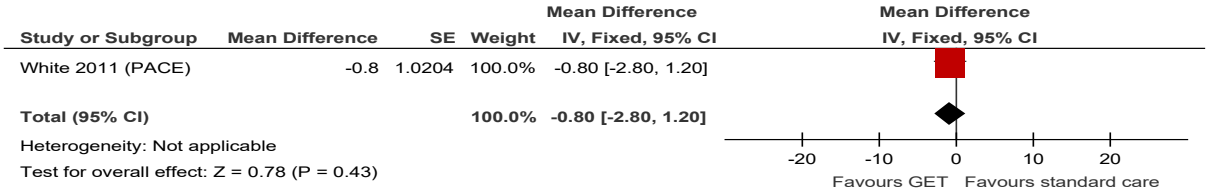


Figure 253: Physical functioning (SF36 physical function) (overall and PEM subgroup results)

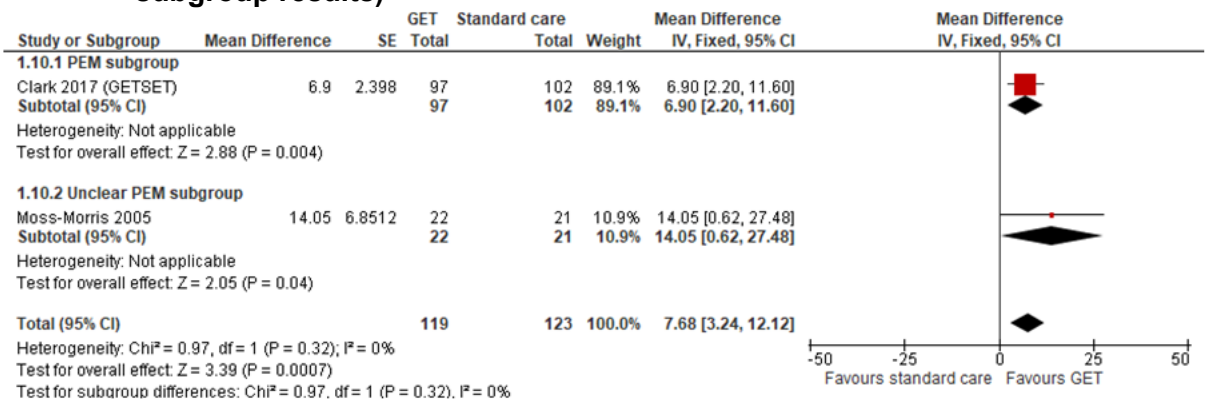


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Figure 254: Physical functioning (SF36 physical function) at 134 weeks

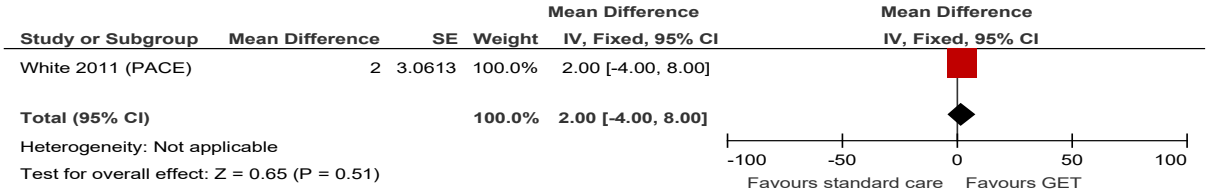

Figure 255: Psychological status (Hospital Anxiety and Depression Scale - depression) (overall and PEM subgroup results)

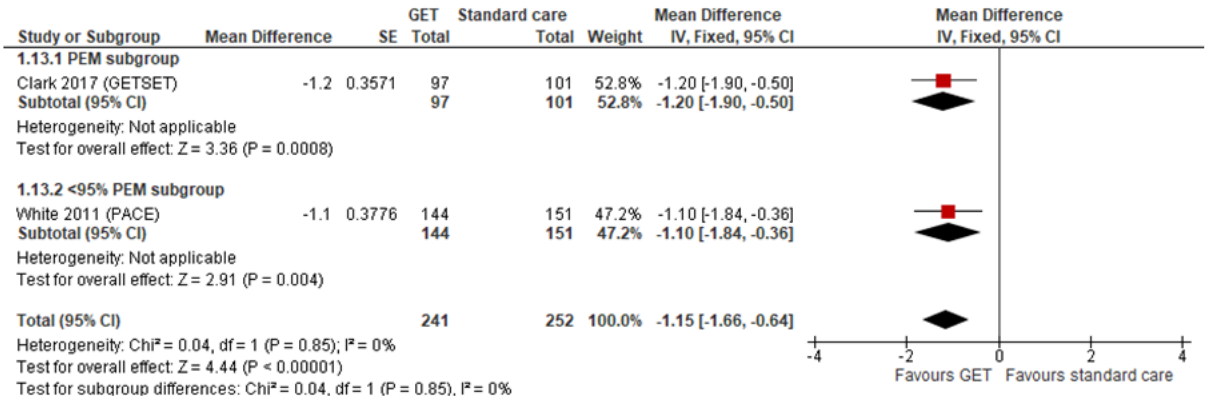

Figure 256: Psychological status (Hospital Anxiety and Depression Scale - anxiety) (overall and PEM subgroup results)

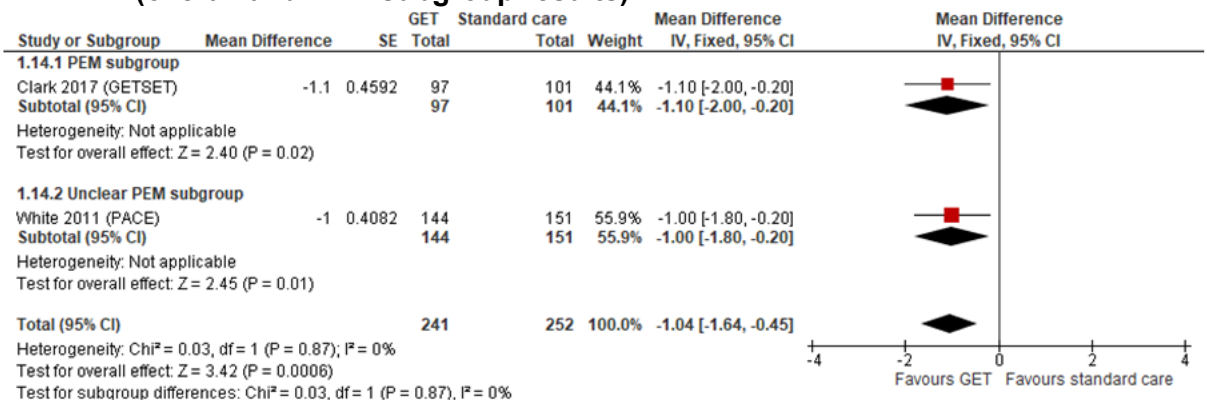

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Figure 257: Pain (numeric rating scale 0-4)

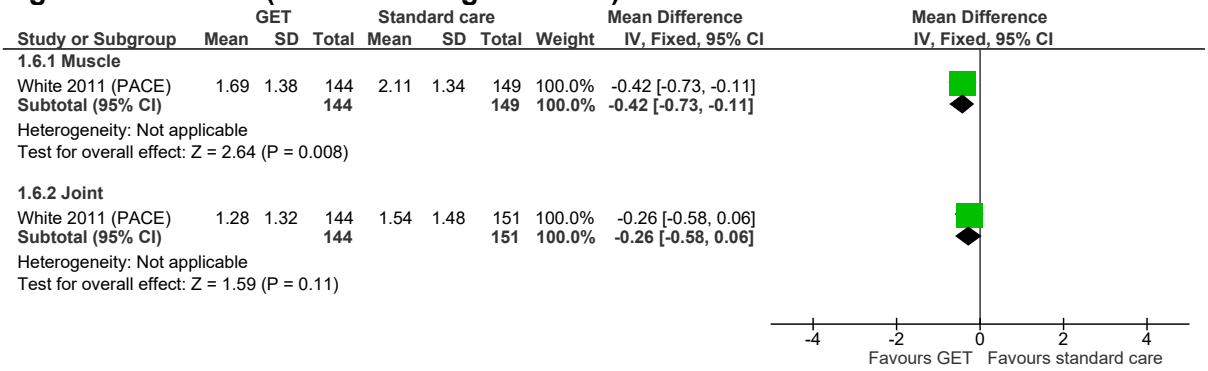

Figure 258: Sleep quality (Jenkins sleep problem questionnaire)

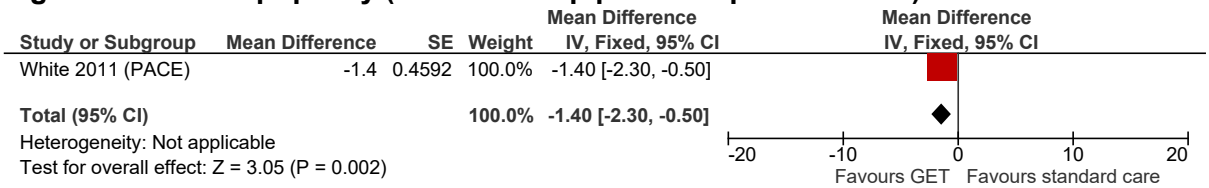

Figure 259: Adverse events (non-serious) (overall and PEM subgroup results)

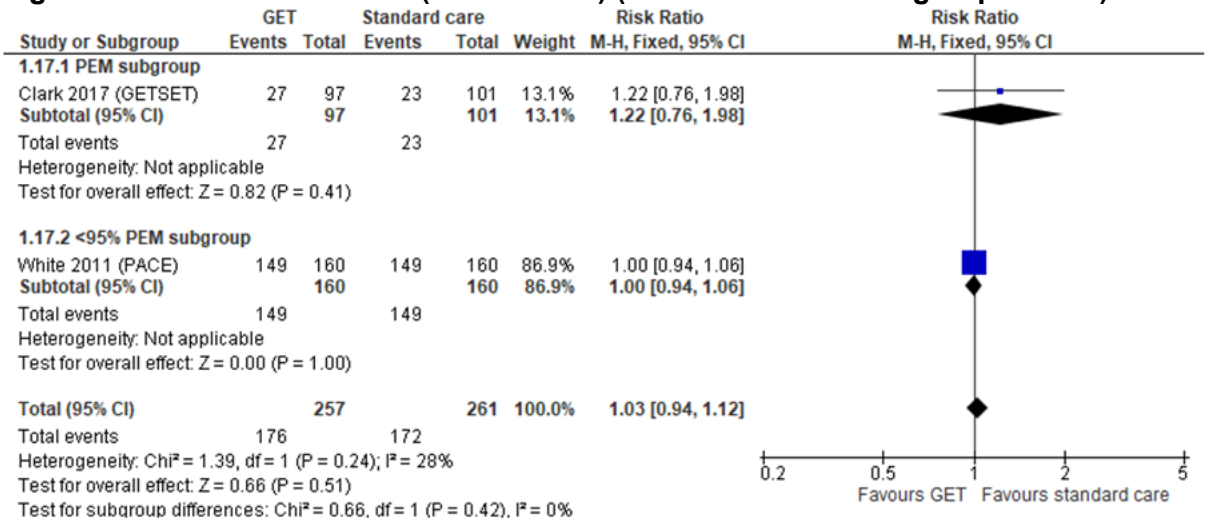

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Figure 260: Adverse events (serious) (overall and PEM subgroup results)

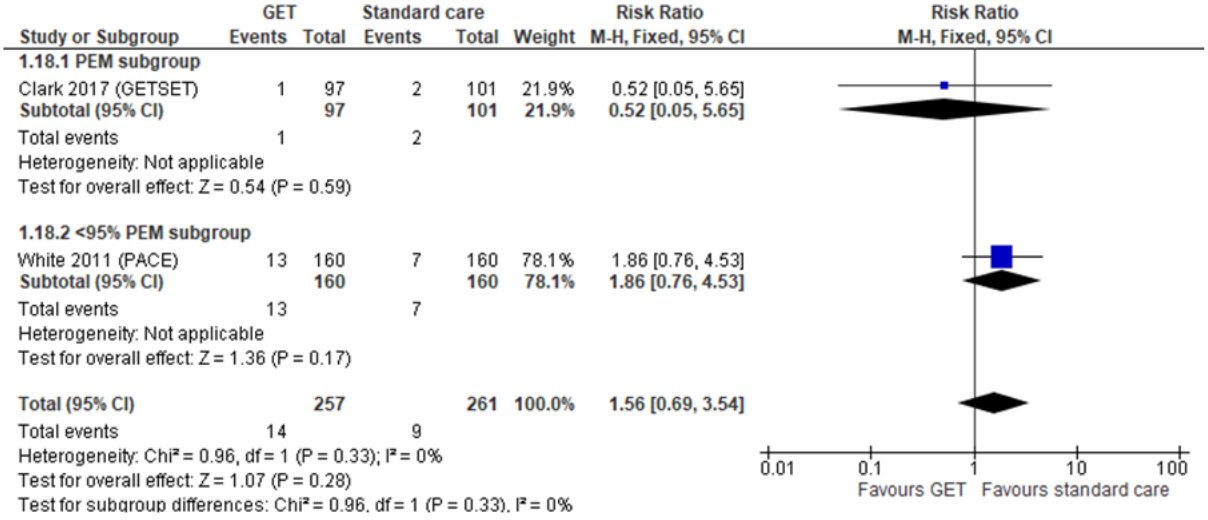

Figure 261: Adverse events (adverse reactions) (overall and PEM subgroup results)

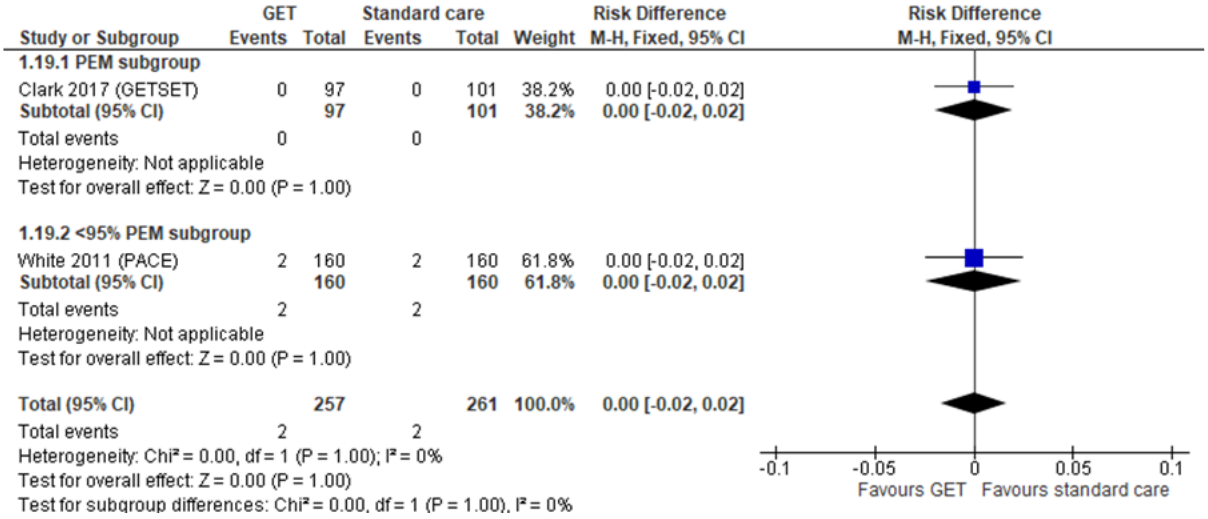

Figure 262: Activity levels (International Physical Activity Questionnaire high vs. low/moderate)

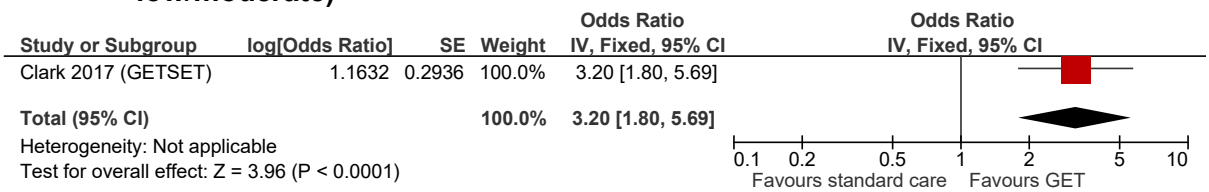

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Figure 263: Return to school/work (Work and Social Adjustment Scale)

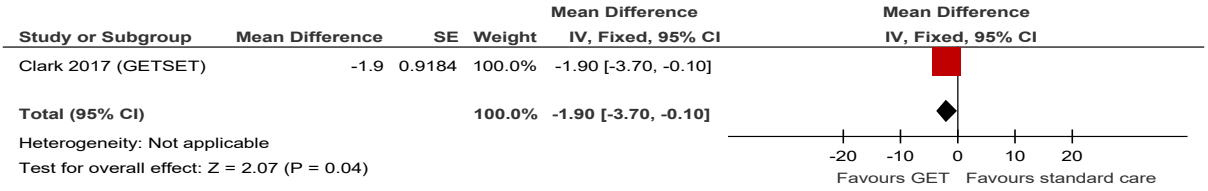

Figure 264: Return to school/work (Work and Social Adjustment Scale) at 134 weeks

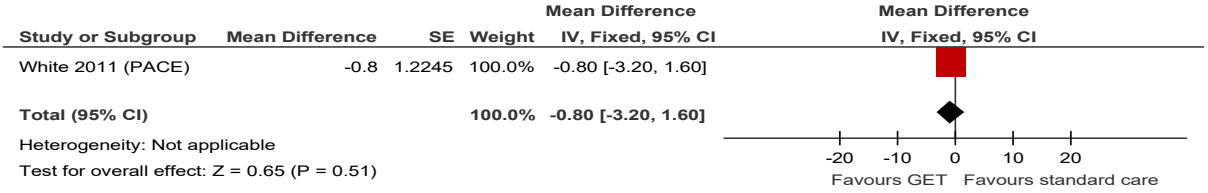

Figure 265: Exercise performance measure (6 minute walk)

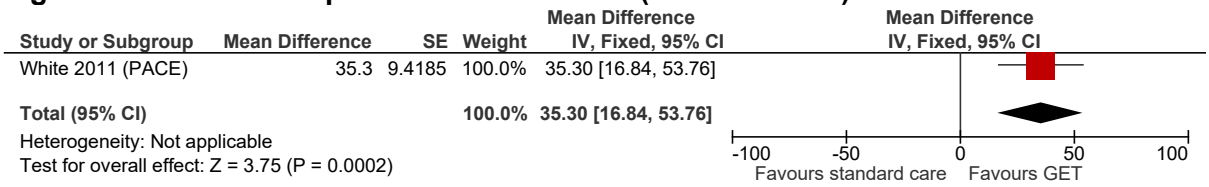

Figure 266: Exercise performance measure (VO2 peak – ml/kg/min)

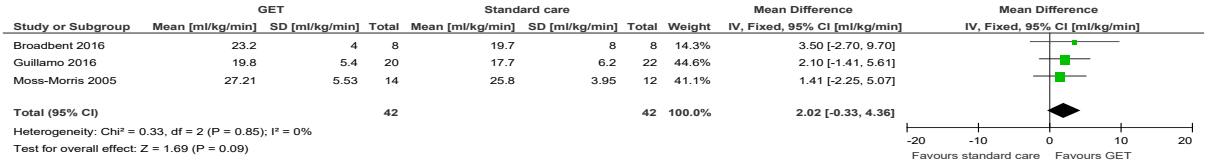

Figure 267: Exercise performance measure (Peak Power - W)

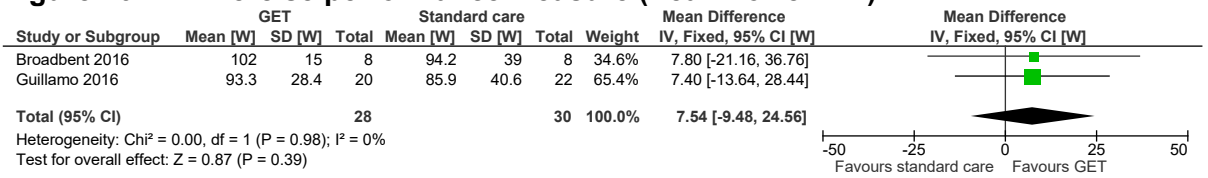

Figure 268: Exercise performance measure (Elapsed exercise time on cycle ergometer – min)

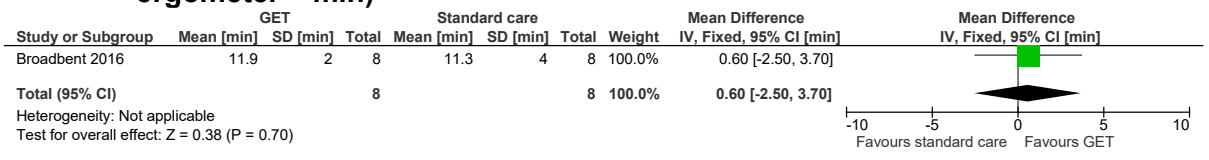

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Figure 269: Exercise performance measure (VE peak – L/min)

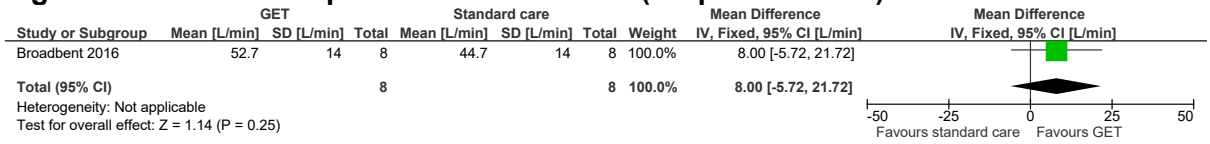
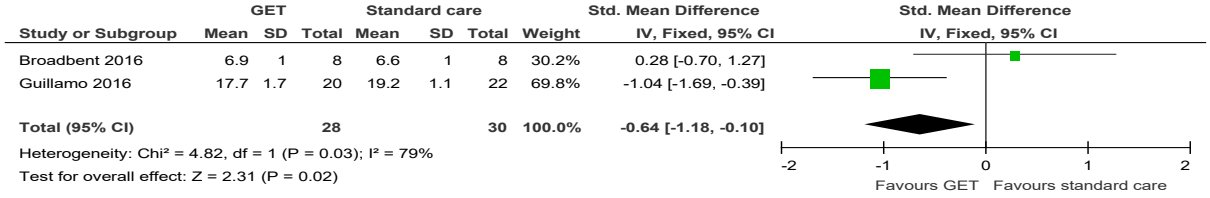


Figure 251: Exercise performance measure (perceived exertion – Borg scale)



E.3.2 Graded exercise therapy versus flexibility/relaxation treatment: adults, severity mixed or unclear

Figure 270: General symptom scales (Clinical global impression of change - much or very much better)

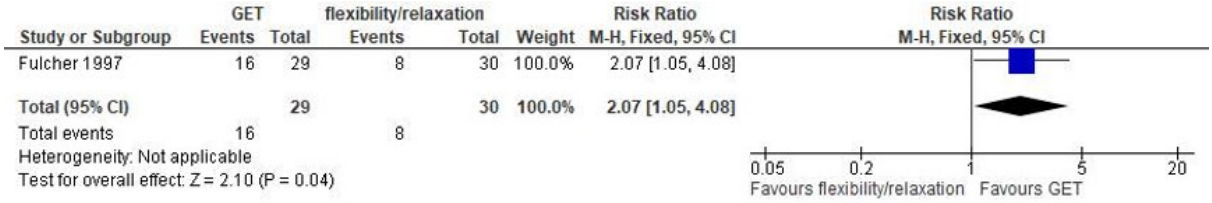


Figure 271: Fatigue/fatigability (Chalder fatigue scale total)

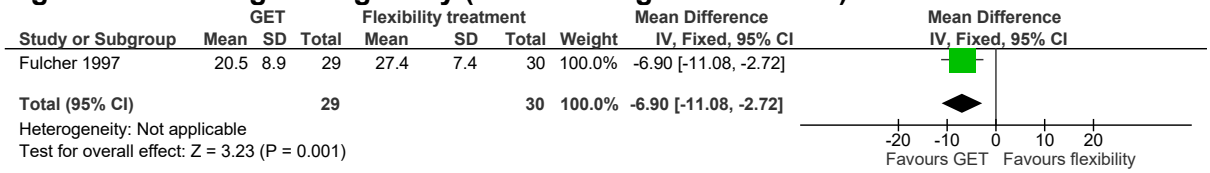


Figure 272: Physical function (SF36 physical function)

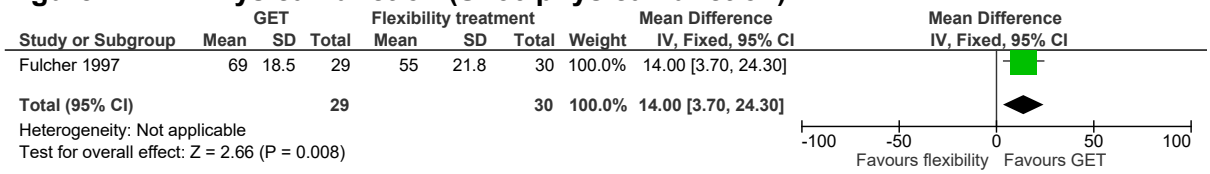


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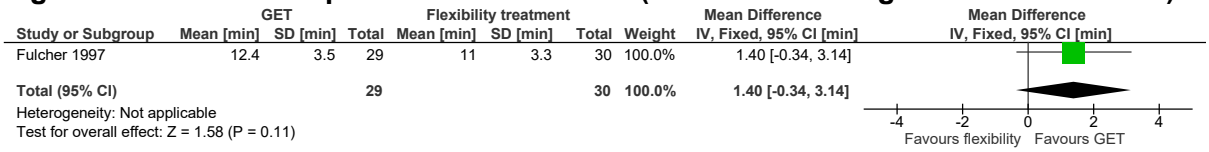
Figure 273: Exercise performance measure (Treadmill walking test duration – min)



E.3.3 Graded exercise therapy versus flexibility/relaxation treatment: age and severity mixed or unclear

Figure 274: General symptom scales (Self-rated global impression of change - much or very much better)

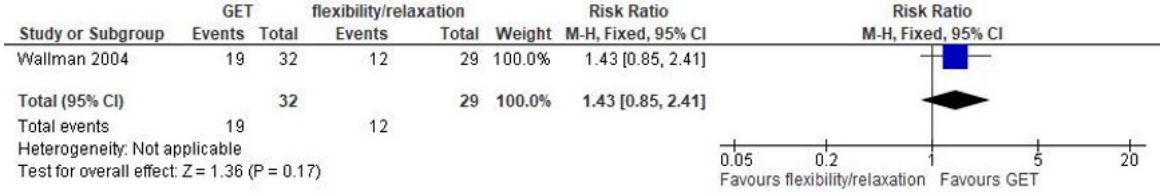


Figure 275: Fatigue/fatigability (Chalder fatigue scale sub scales)

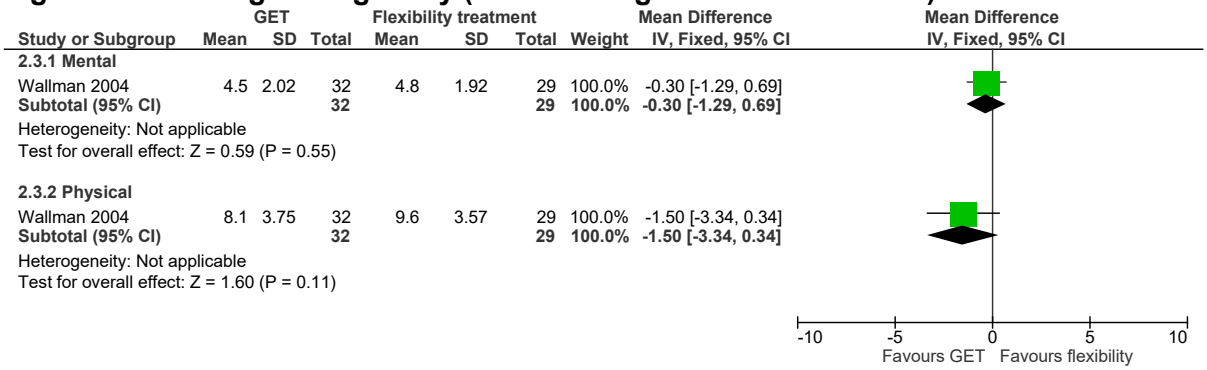


Figure 276: Cognitive function (Stroop test)

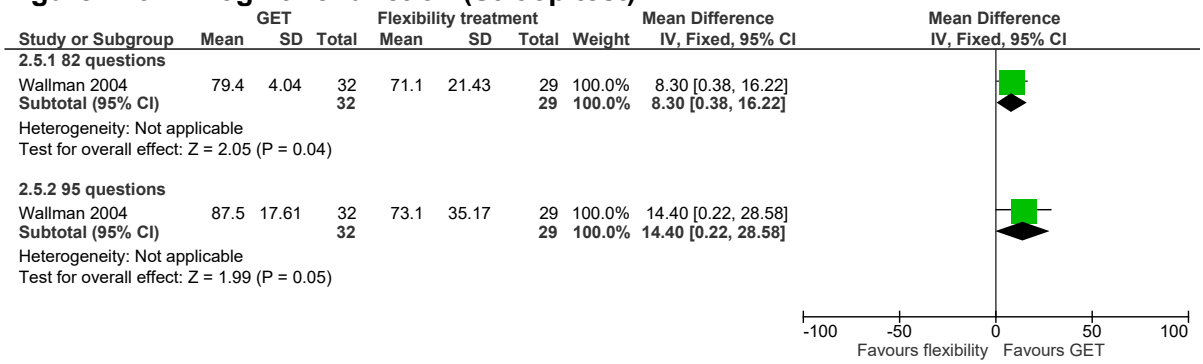


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Figure 277: Psychological status (Hospital Anxiety and Depression Scale - depression)

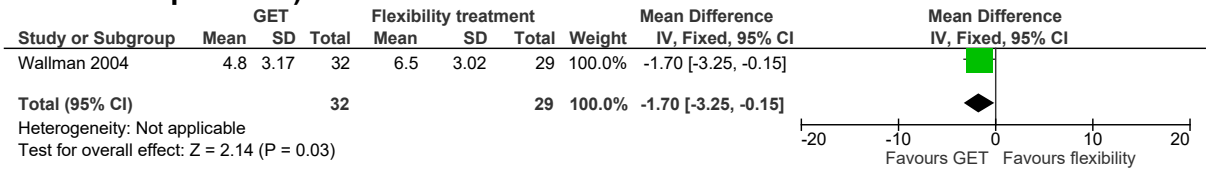


Figure 278: Psychological status (Hospital Anxiety and Depression Scale - anxiety)

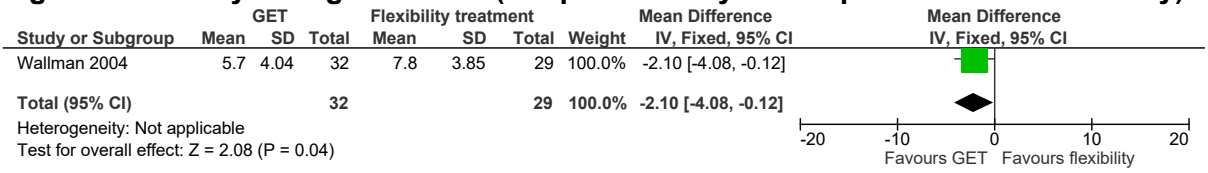
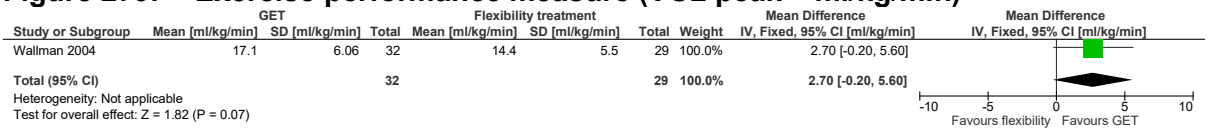


Figure 279: Exercise performance measure (VO2 peak – ml/kg/min)



E.3.4 Graded exercise therapy versus heart rate variability biofeedback therapy: adults, severity mixed or unclear

Figure 280: Quality of life (SF36)

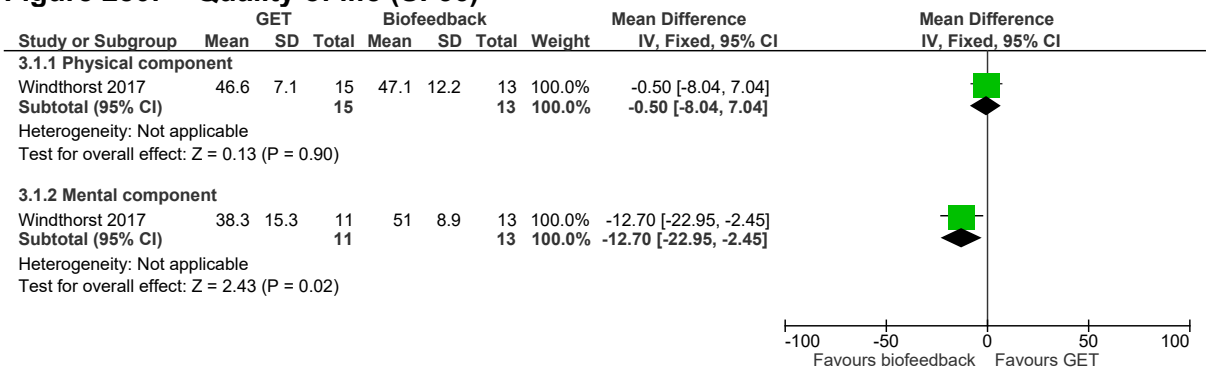


Figure 281: Fatigue/fatigability (Multidimensional Fatigue Inventory)

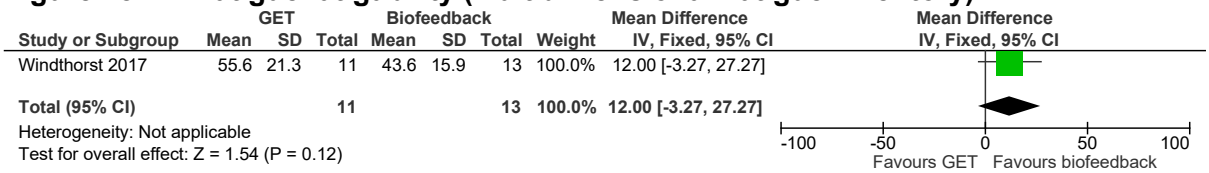


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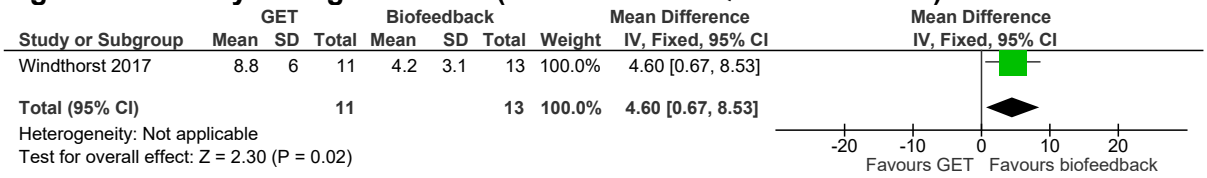
Figure 282: Psychological status (Patient Health Questionnaire-9)



E.3.5 Graded exercise therapy versus adaptive pacing therapy: adults, severity mixed or unclear

Figure 283: Quality of life (EQ5D)

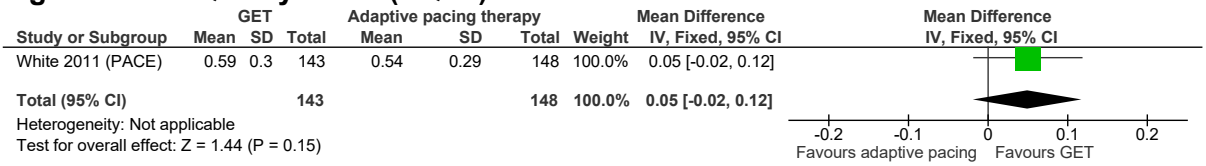


Figure 284: General symptom scales (Clinical global impression of change positive vs. negative/minimal change) @ 134 weeks

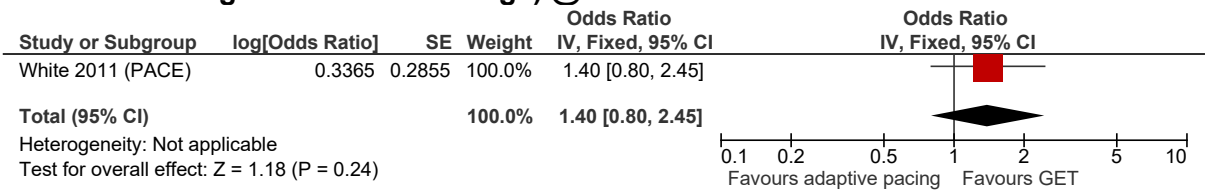


Figure 285: Fatigue/fatigability (Chalder fatigue scale) @ 134 weeks

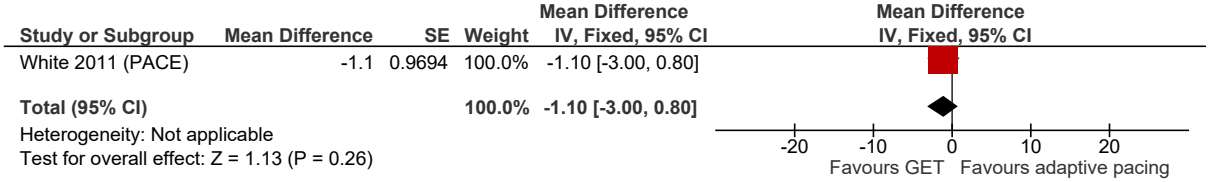


Figure 286: Physical functioning (SF36 physical function) @ 134 weeks

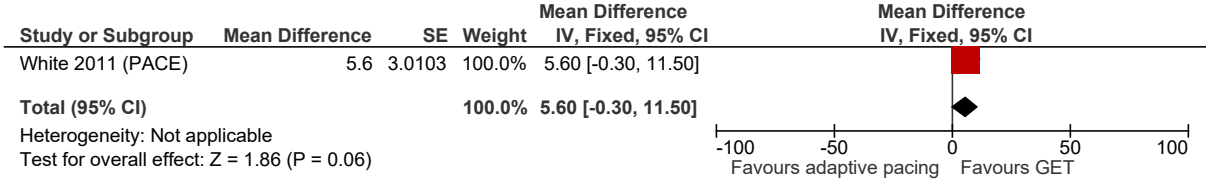


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Figure 287: Psychological status (Hospital anxiety and depression scale - depression)

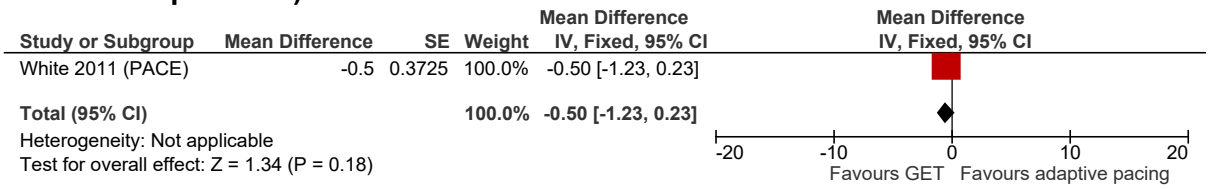

Figure 288: Psychological status (Hospital anxiety and depression scale - anxiety)

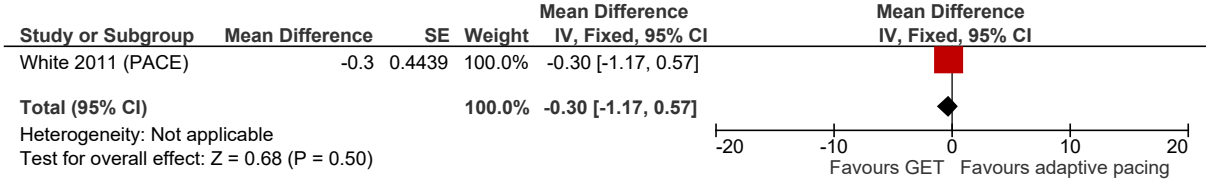

Figure 289: Pain (NRS 0-4)

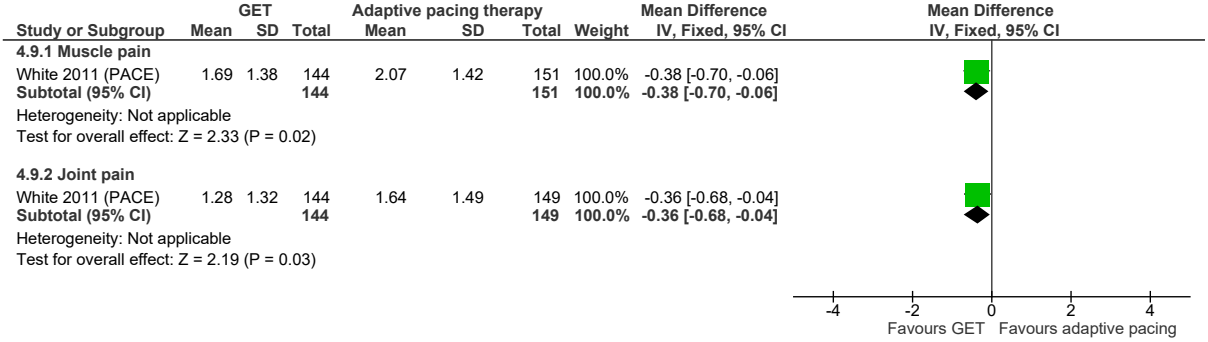

Figure 290: Sleep quality (Jenkins sleep scale)

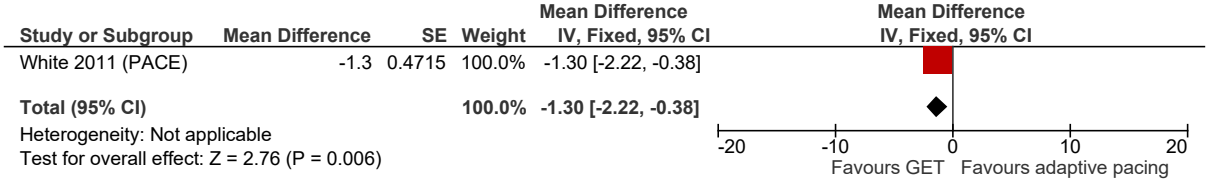

Figure 291: Adverse events (non-serious)

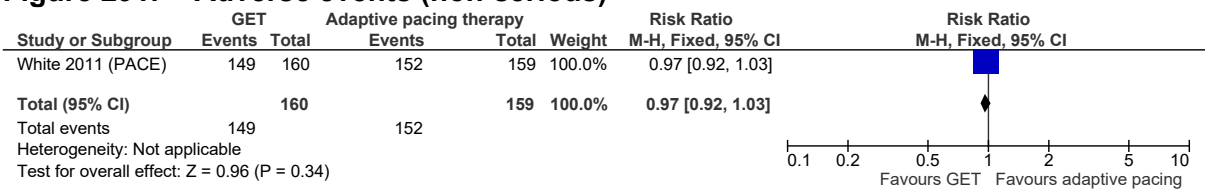

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Figure 292: Adverse events (serious)

Study or Subgroup	GET Events	GET Total	Adaptive pacing therapy Events	Adaptive pacing therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
White 2011 (PACE)	13	160	15	159	100.0%	0.86 [0.42, 1.75]
Total (95% CI)		**160**		**159**	**100.0%**	**0.86 [0.42, 1.75]**
Total events	13		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

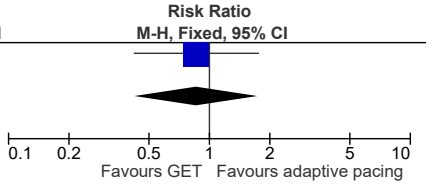


Figure 293: Adverse events (adverse reactions)

Study or Subgroup	GET Events	GET Total	Adaptive pacing therapy Events	Adaptive pacing therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
White 2011 (PACE)	2	160	2	159	100.0%	0.99 [0.14, 6.97]
Total (95% CI)		**160**		**159**	**100.0%**	**0.99 [0.14, 6.97]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)

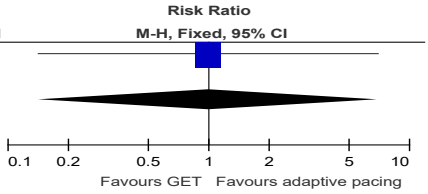


Figure 294: Return to school/work (Work and social adjustment scale) @ 134 weeks

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
White 2011 (PACE)	-2.1	1.2245	100.0%	-2.10 [-4.50, 0.30]
Total (95% CI)			**100.0%**	**-2.10 [-4.50, 0.30]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)

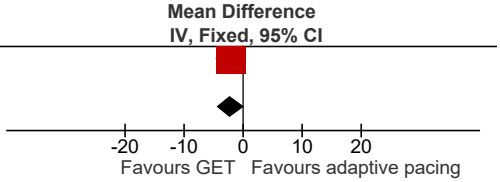
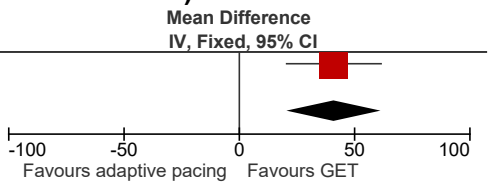


Figure 295: Exercise performance measure (6 minute walk test)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
White 2011 (PACE)	41	10.4441	100.0%	41.00 [20.53, 61.47]
Total (95% CI)			**100.0%**	**41.00 [20.53, 61.47]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.93 (P < 0.0001)



E.3.6 GET versus Intermittent exercise: adults, severity mixed or unclear

Figure 296: Exercise performance measure (VO2 peak – ml/kg/min)

Study or Subgroup	GET Mean [ml/kg/min]	GET SD [ml/kg/min]	GET Total	IE Mean [ml/kg/min]	IE SD [ml/kg/min]	IE Total	Weight	Mean Difference IV, Fixed, 95% CI [ml/kg/min]
Broadbent 2016	23.2	4	8	24.5	7	8	100.0%	-1.30 [-6.89, 4.29]
Total (95% CI)			**8**			**8**	**100.0%**	**-1.30 [-6.89, 4.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

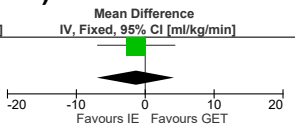


Figure 297: Exercise performance measure (Peak power – W)

Study or Subgroup	GET Mean [W]	GET SD [W]	GET Total	IE Mean [W]	IE SD [W]	IE Total	Weight	Mean Difference IV, Fixed, 95% CI [W]
Broadbent 2016	102	15	8	108.8	12	8	100.0%	-6.80 [-20.11, 6.51]
Total (95% CI)			**8**			**8**	**100.0%**	**-6.80 [-20.11, 6.51]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

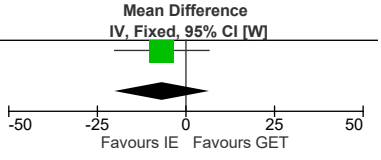


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Figure 298: Exercise performance measure (Elapsed exercise time on cycle ergometer – min)

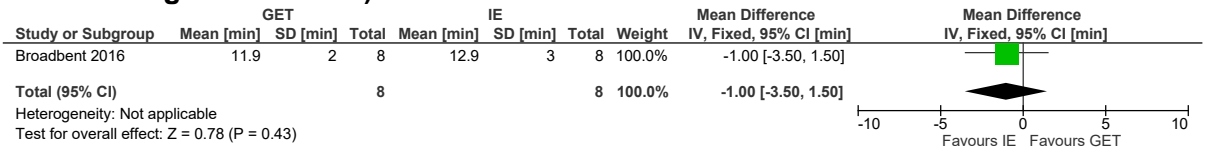


Figure 299: Exercise performance measure (VE peak – L/min)

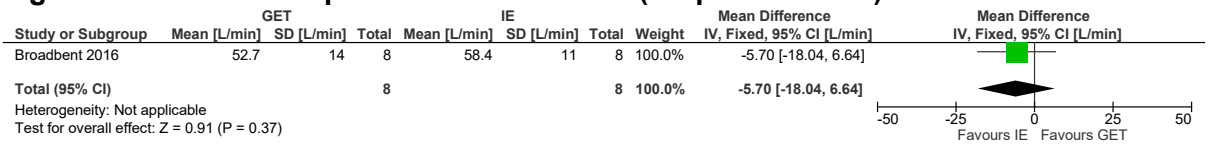
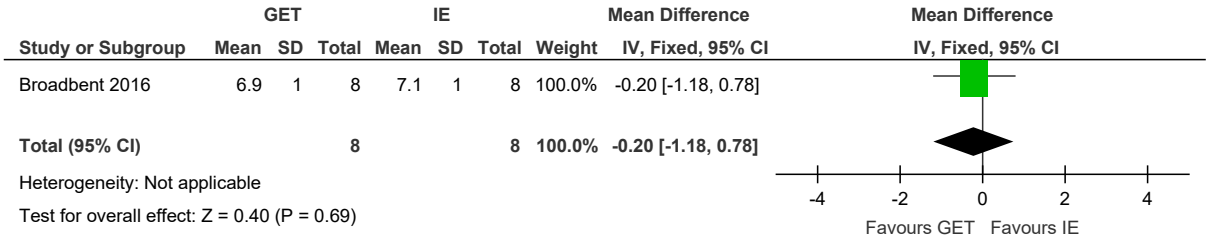


Figure 300: Exercise performance measure (Rated perceived exertion/modified Borg scale)



E.3.7 GET versus Activity diaries: adults, severity mixed or unclear

Figure 301: Fatigue (Chalder fatigue scale – change scores)

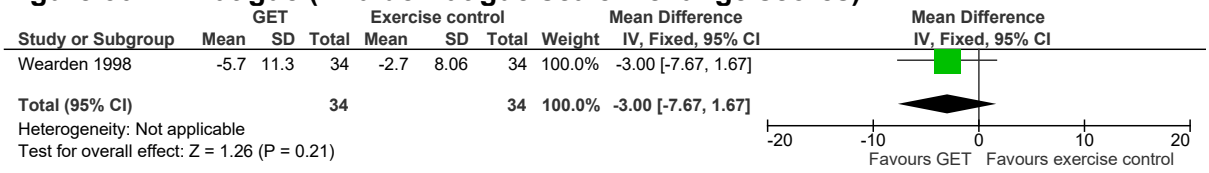


Figure 302: Psychological status (Hospital anxiety and depression scale – depression – change scores)

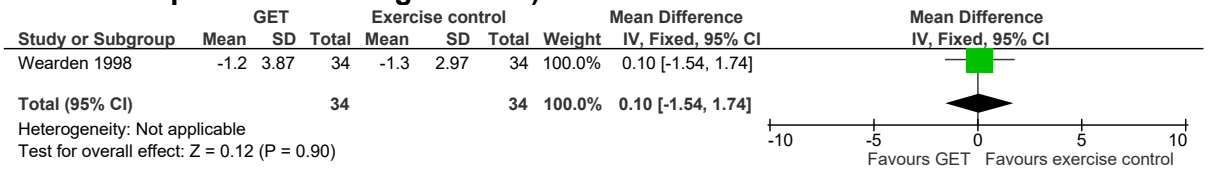


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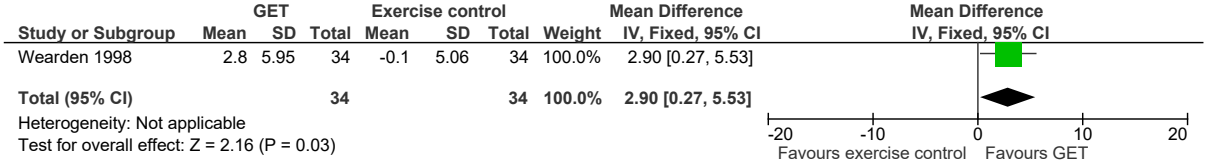
Figure 303: Exercise performance measure (VO2 peak – ml/kg/min – change scores)



E.3.8 Graded exercise therapy versus standard care: age and severity mixed or unclear

Figure 304: Fatigue/fatigability (Chalder fatigue questionnaire)

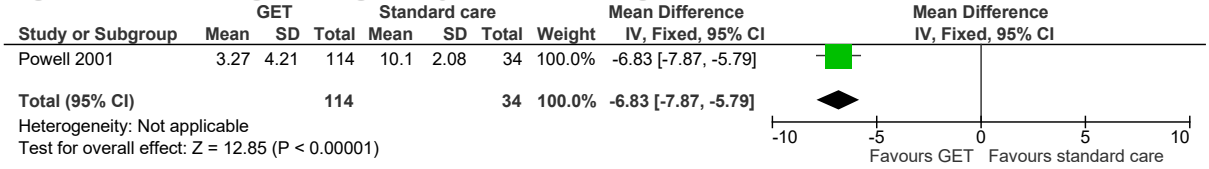


Figure 305: Sleep quality (Sleep problem questionnaire)

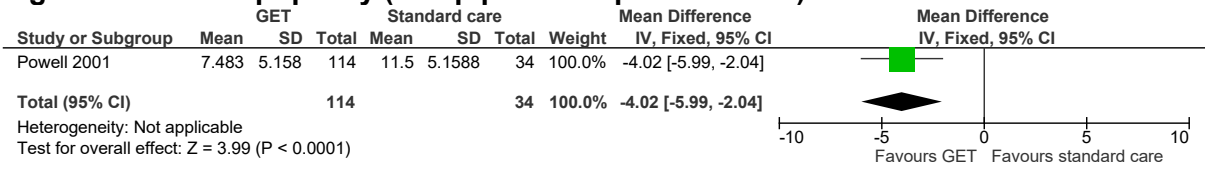


Figure 306: Psychological status (Hospital anxiety and depression scale)

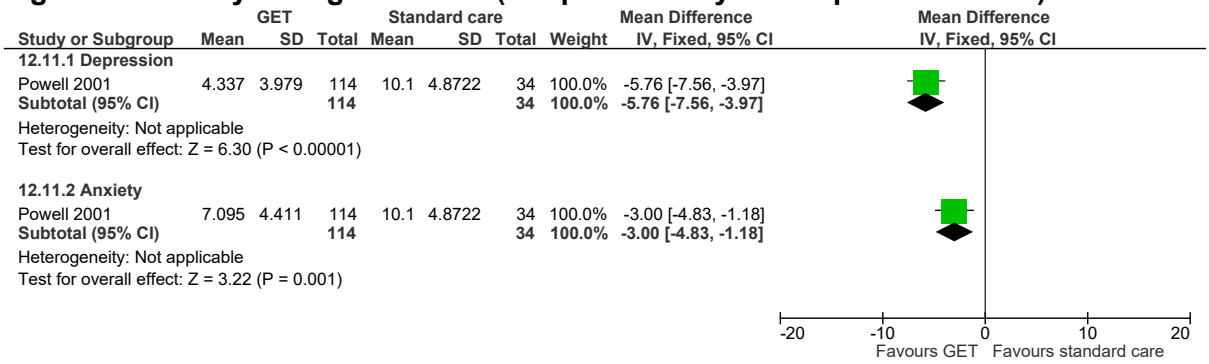
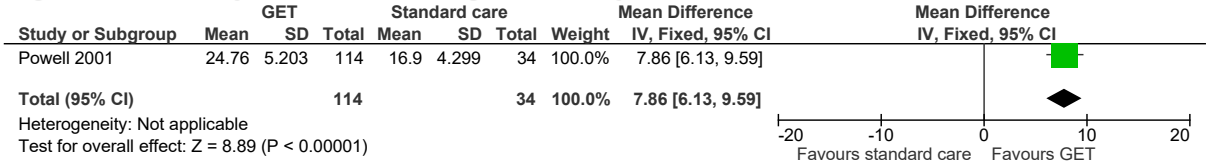


Figure 307: Physical functioning (SF36 physical function)



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Other exercise interventions

E.3.9 Intermittent exercise versus standard care: adults, severity mixed or unclear

Figure 308: Exercise performance measure (VO2 peak – ml/kg/min)

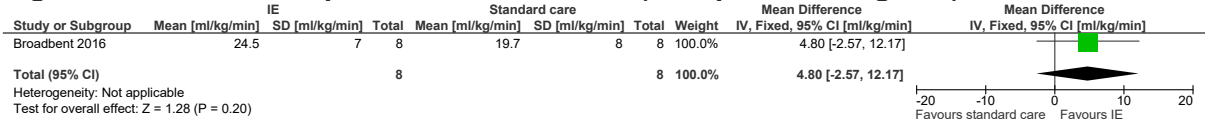


Figure 309: Exercise performance measure (Peak power – W)

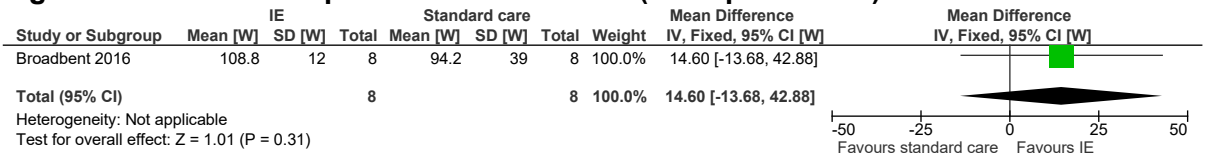


Figure 310: Exercise performance measure (Elapsed exercise time on cycle ergometer – min)

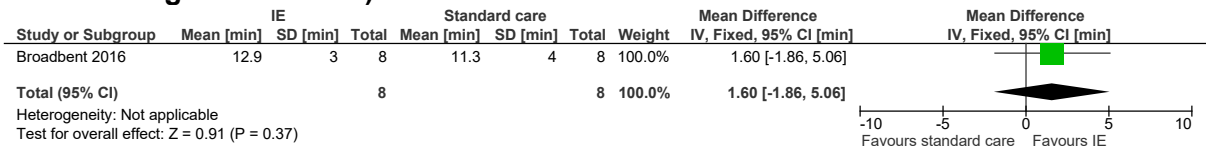


Figure 311: Exercise performance measure (VE peak – L/min)

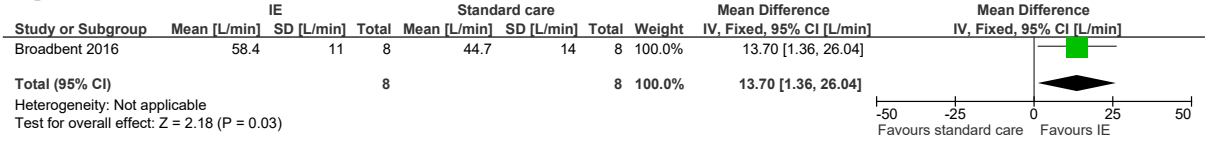
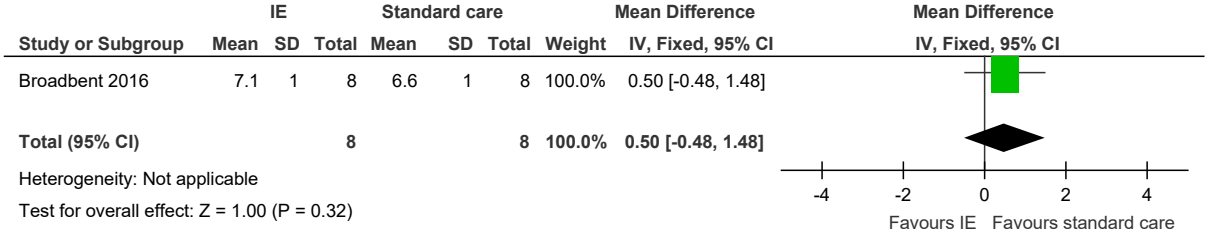


Figure 312: Exercise performance measure (Rated perceived exertion/modified Borg scale)



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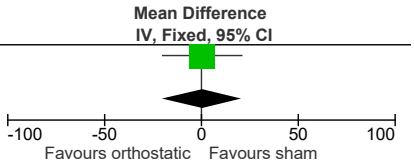
E.3.10 Orthostatic training versus sham: adults, severity mixed or unclear

Figure 313: Fatigue/fatigability (Fatigue Impact Scale)

Study or Subgroup	Orthostatic training Mean	SD	Total	Sham Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sutcliffe 2010	92.9	35.9	18	92.5	25.8	18	100.0%	0.40 [-20.02, 20.82]
Total (95% CI)			**18**			**18**	**100.0%**	**0.40 [-20.02, 20.82]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)



E.3.11 Qigong versus no treatment: adults, severity mixed or unclear

Figure 314: Quality of life (SF36 sub scales) - change scores

Study or Subgroup	Qigong Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.1.1 Mental health								
Dybwad 2007	7.2	17	14	-5	18	14	100.0%	12.20 [-0.77, 25.17]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**12.20 [-0.77, 25.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
7.1.2 Vitality								
Dybwad 2007	4.7	17	14	6.6	17	14	100.0%	-1.90 [-14.49, 10.69]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-1.90 [-14.49, 10.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.77)								
7.1.3 Bodily pain								
Dybwad 2007	13.3	25	14	0.4	18	14	100.0%	12.90 [-3.24, 29.04]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**12.90 [-3.24, 29.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.57 (P = 0.12)								
7.1.4 General health								
Dybwad 2007	-2.5	21	14	4.5	14	14	100.0%	-7.00 [-20.22, 6.22]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-7.00 [-20.22, 6.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.04 (P = 0.30)								
7.1.5 Social functioning								
Dybwad 2007	5	33	14	5.5	25	14	100.0%	-0.50 [-22.19, 21.19]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-0.50 [-22.19, 21.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.05 (P = 0.96)								
7.1.6 Role emotional								
Dybwad 2007	11.1	47	14	-4.2	58	14	100.0%	15.30 [-23.80, 54.40]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**15.30 [-23.80, 54.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								
7.1.7 Physical functioning								
Dybwad 2007	1.3	16	14	4.7	13	14	100.0%	-3.40 [-14.20, 7.40]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-3.40 [-14.20, 7.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.54)								
7.1.8 Role physical								
Dybwad 2007	3.3	30	14	1.6	21	14	100.0%	1.70 [-17.48, 20.88]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**1.70 [-17.48, 20.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.86)								

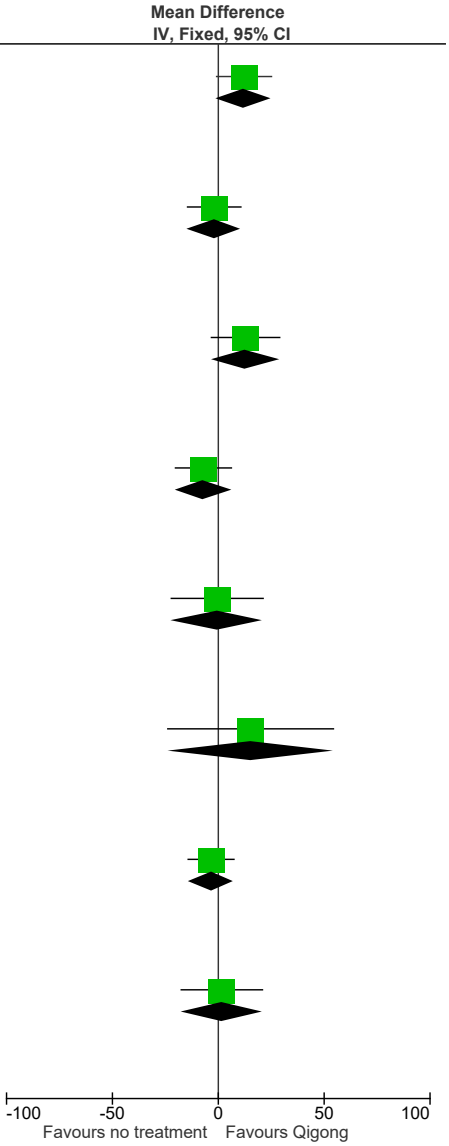


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Figure 315: Fatigue (fatigue severity scale)

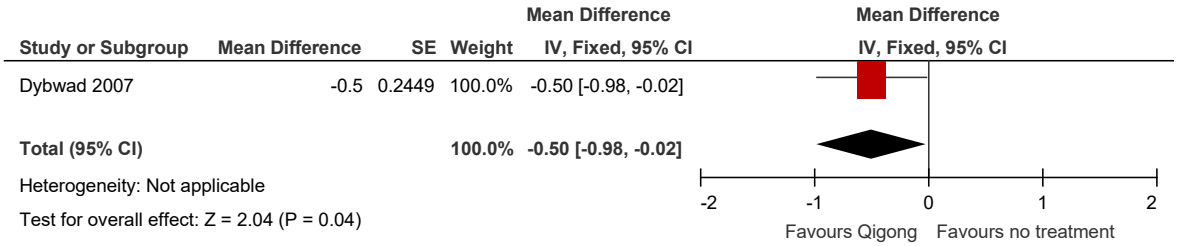


Figure 316: Exercise performance measure (VO2 max- ml/kg/min)

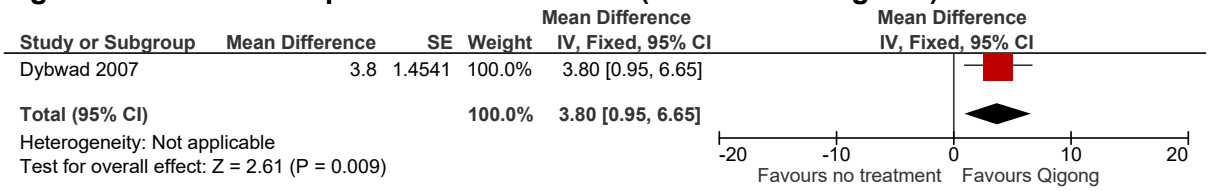


Figure 317: Exercise performance measure (Max workload)

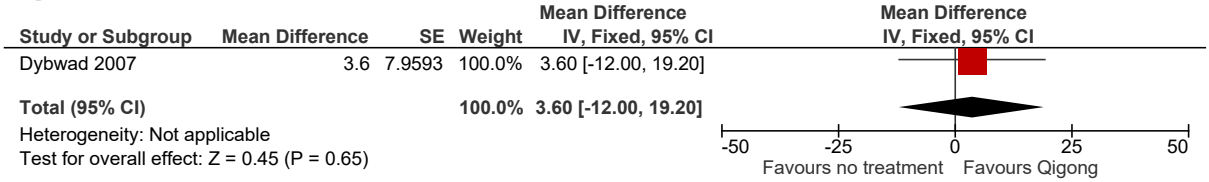
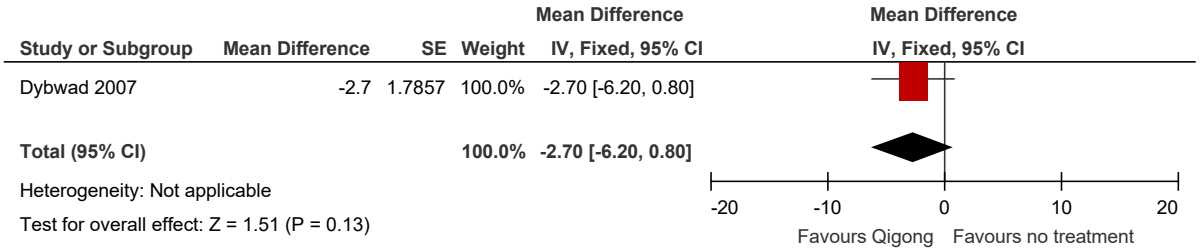
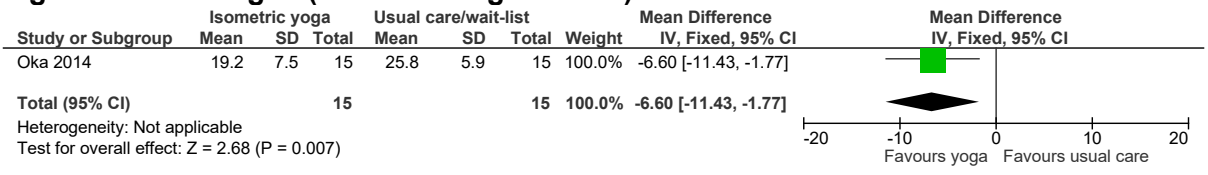


Figure 318: Exercise performance measure (Borg scale – rating of perceived exertion)



E.3.12 Isometric yoga versus Usual care: adults, severity mixed or unclear

Figure 319: Fatigue (Chalder Fatigue Scale)



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E.3.13 Anaerobic activity therapy versus cognitive therapy: adults, moderate severity

Figure 320: Quality of life (Quality of life scale)

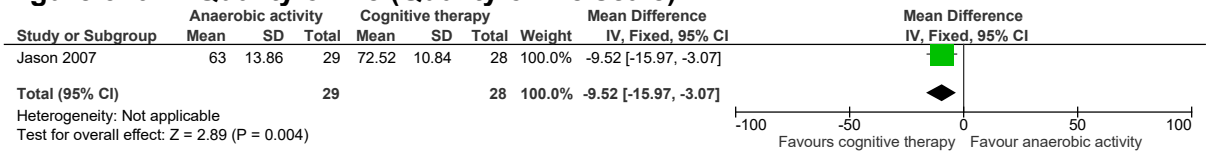

Figure 321: General symptom scales (participant global impression of change - improved/much/very much improved)

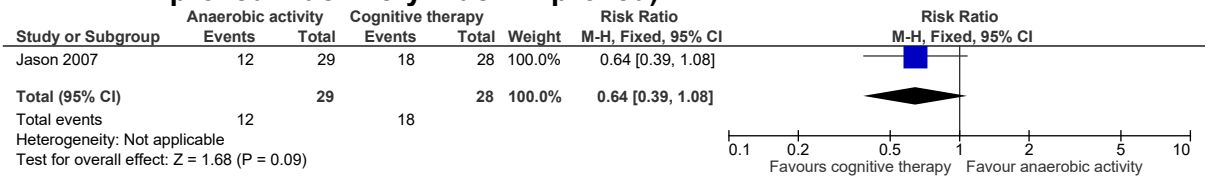

Figure 322: Fatigue/fatigability (Fatigue severity scale)

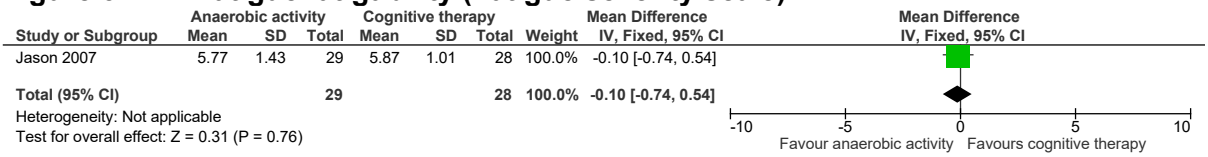

Figure 323: Physical functioning (SF36 physical function)

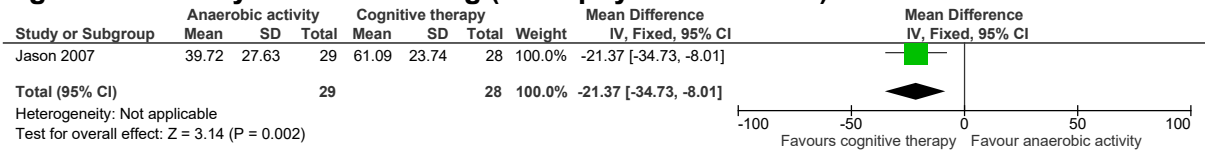

Figure 324: Psychological status (Beck depression inventory)

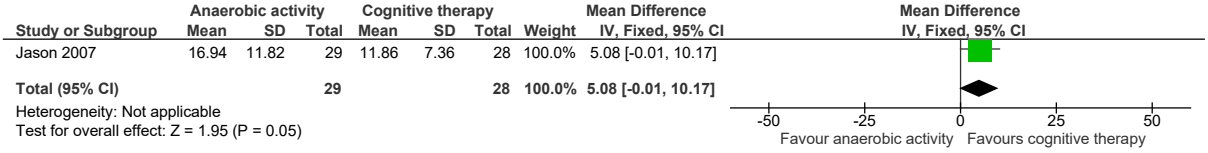

Figure 325: Psychological status (Beck anxiety inventory)

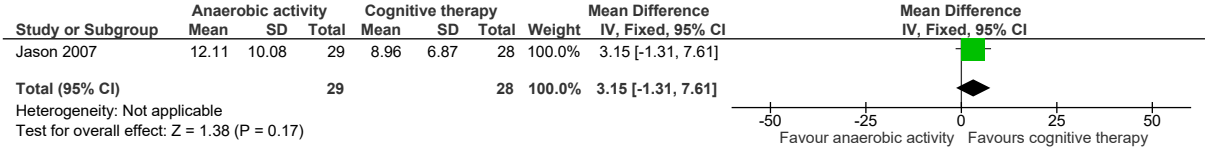

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Figure 326: Return to school/work (employment)

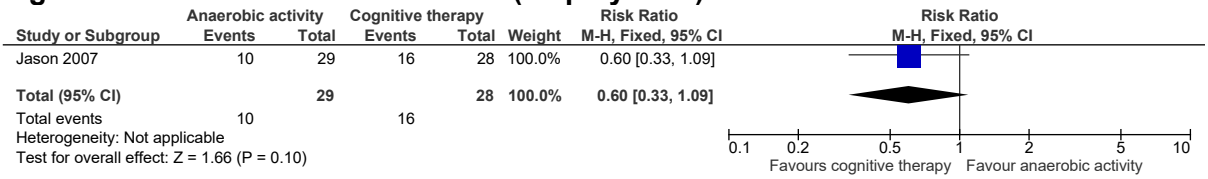


Figure 327: Exercise performance measure (6 minute walk test)

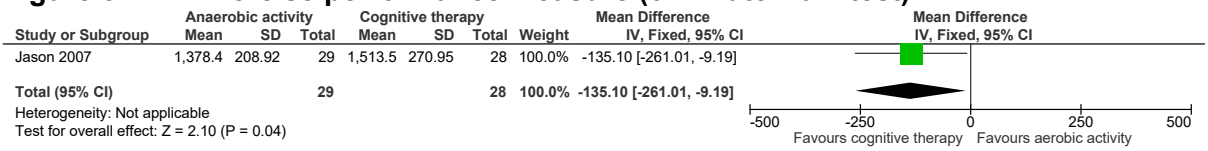


Figure 328: Pain (Brief pain inventory - severity)

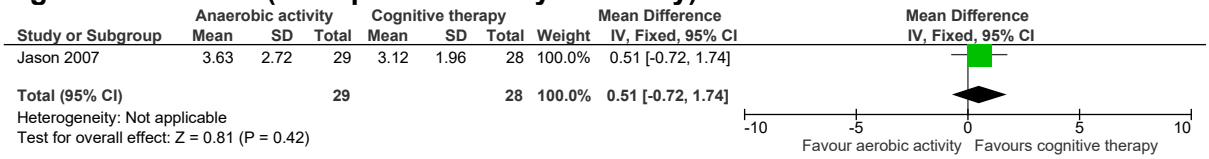


Figure 329: Pain (Brief Pain Inventory - interference)

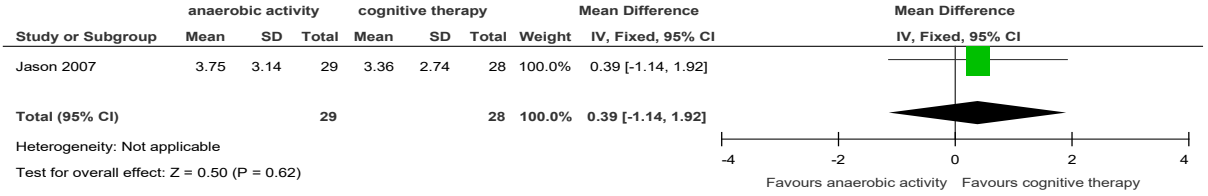
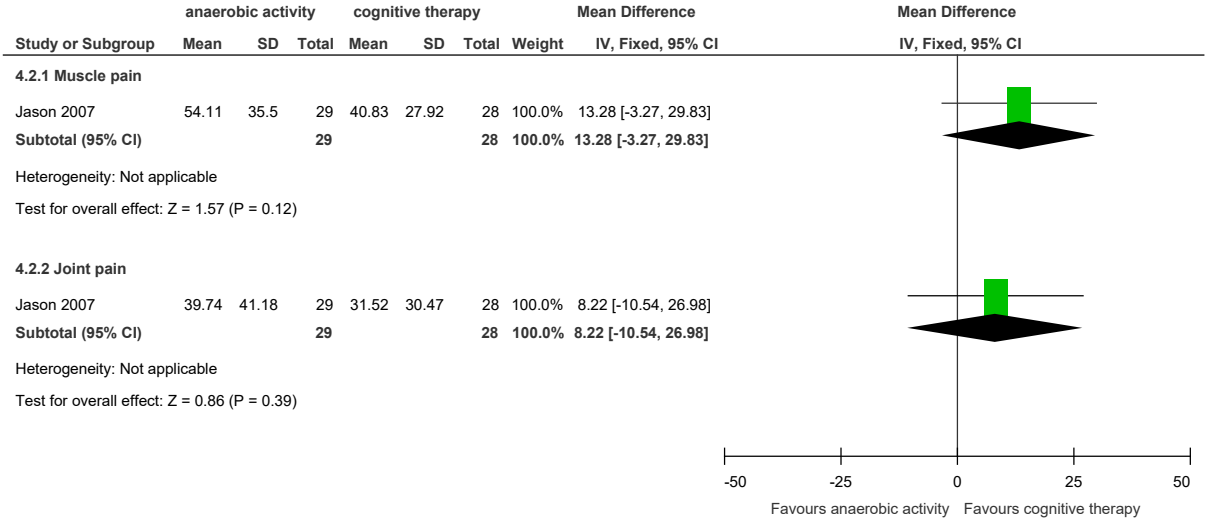


Figure 330: Pain (Muscle pain & joint pain numeric rating scale)



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E.3.14 Anaerobic activity therapy versus relaxation techniques: adults, moderate severity

Figure 331: Quality of life (Quality of life scale)

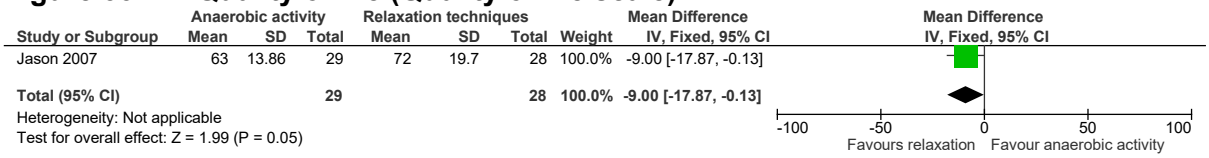

Figure 332: General symptom scales (participant global impression of change - improved/much/very much improved)

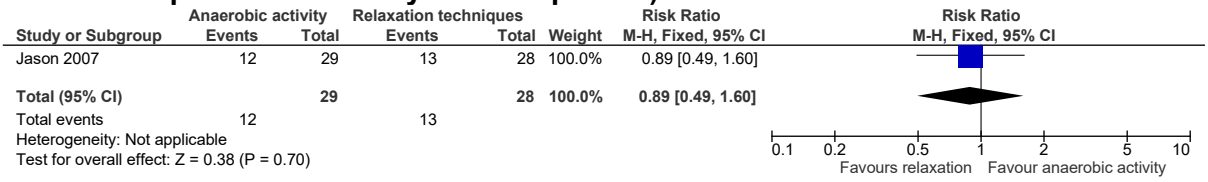

Figure 333: Fatigue/fatigability (Fatigue severity scale)

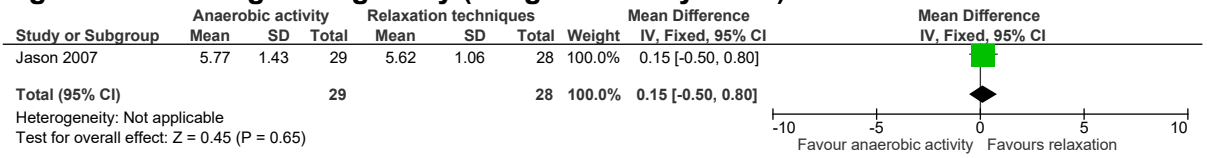

Figure 334: Physical functioning (SF36 physical function)

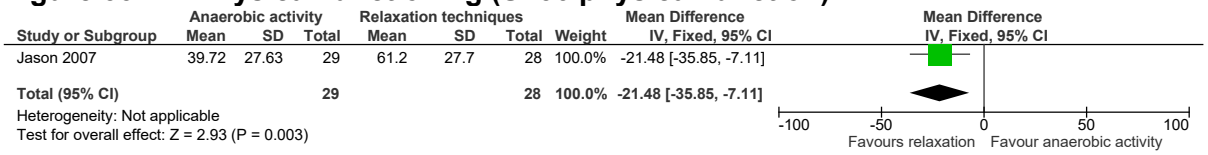

Figure 335: Psychological status (Beck depression inventory)

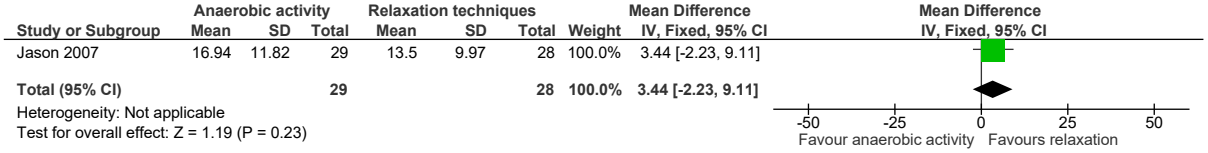

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Figure 336: Psychological status (Beck anxiety inventory)

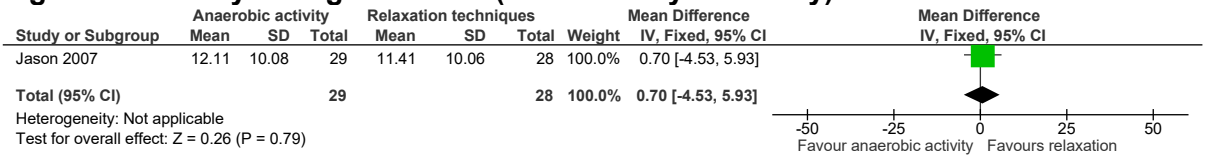

Figure 337: Return to school/work (employment)

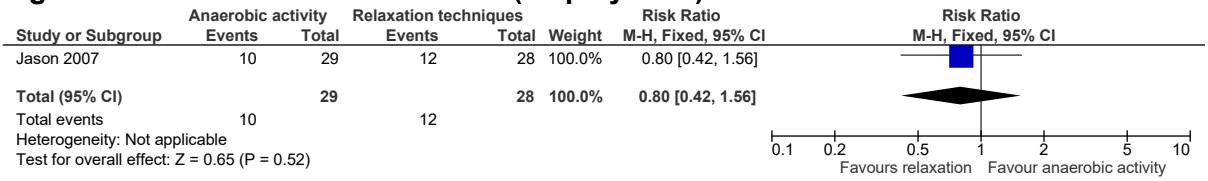

Figure 338: Exercise performance measure (6 minute walk test)

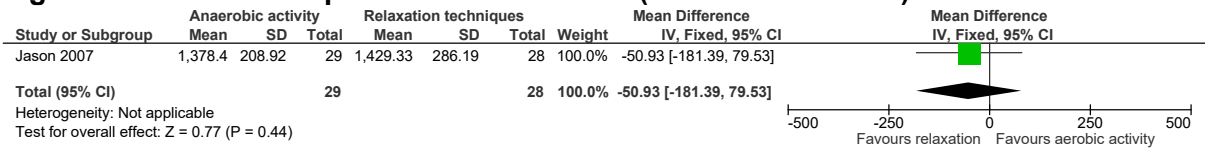

Figure 339: Pain (Brief pain inventory - severity)

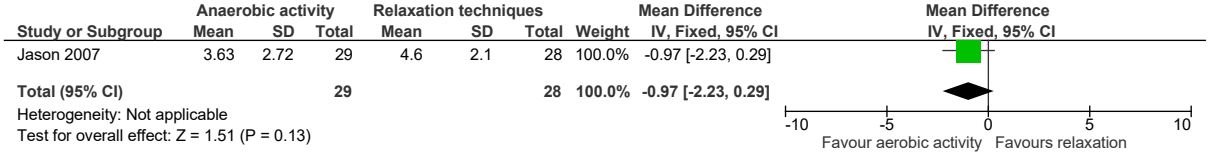

Figure 340: Pain (Brief Pain Inventory - interference)

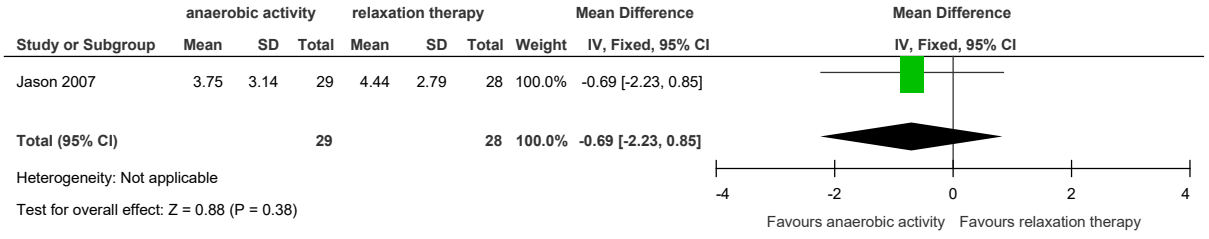

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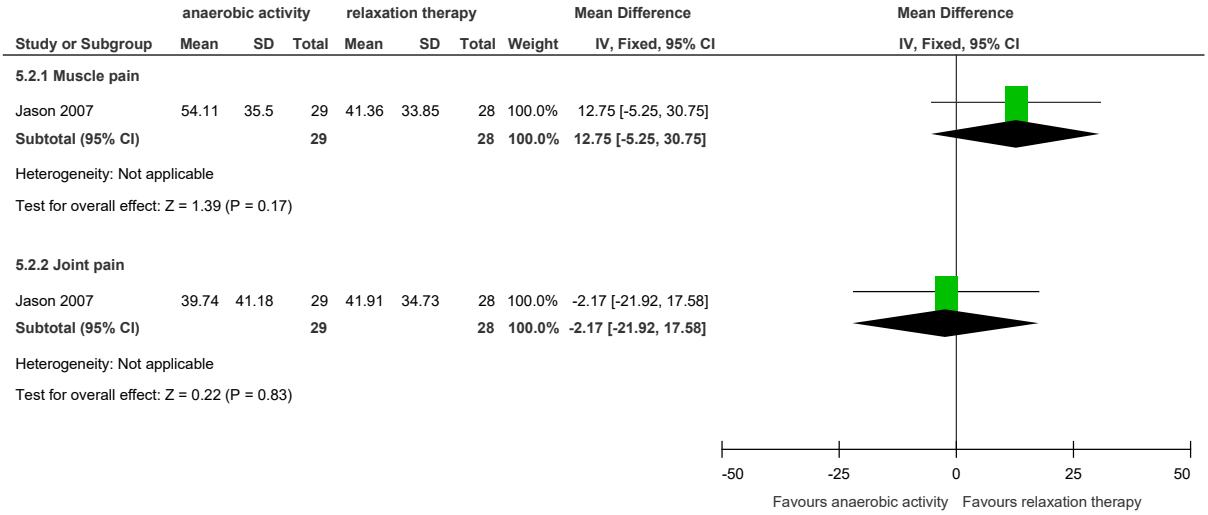
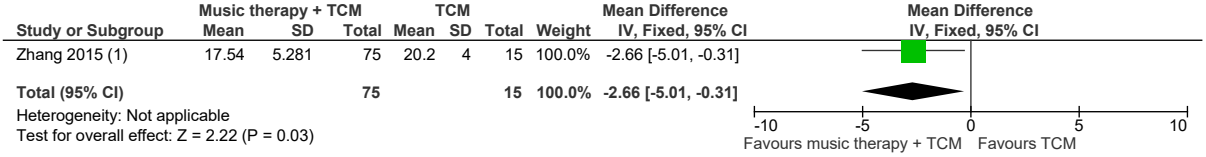
Figure 341: Pain (Muscle pain & joint paint numeric rating scale)



E.4 Complementary therapies

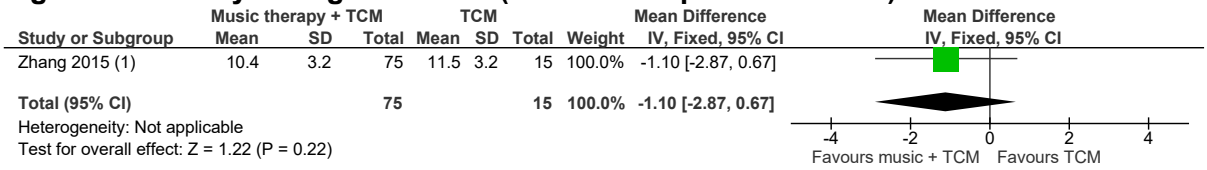
E.4.1 Music therapy and Traditional Chinese Medicine versus Traditional Chinese Medicine: age and severity mixed or unclear

Figure 342: Fatigue (Fatigue Scale based on Chalder Fatigue Scale)



Footnotes
(1) Music therapy = five elements music therapy, 5 arms combined; TCM = Lixujieyu recipe

Figure 343: Psychological Status (Hamilton Depression Scale)



Footnotes
(1) Music therapy = five elements music therapy, 5 arms combined; TCM = Lixujieyu recipe

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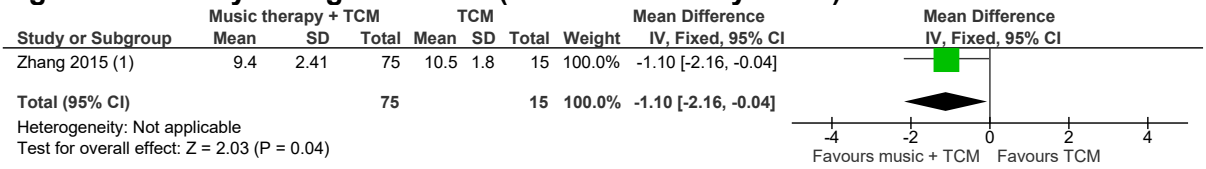
Figure 344: Psychological Status (Hamilton Anxiety Scale)



Footnotes
(1) Music therapy = five elements music therapy, 5 arms combined; TCM = Lixujieyu recipe

E.4.2 Homeopathy versus Placebo: adults, severity mixed or unclear

Figure 345: Quality of life (Functional Limitations Profile) – change scores

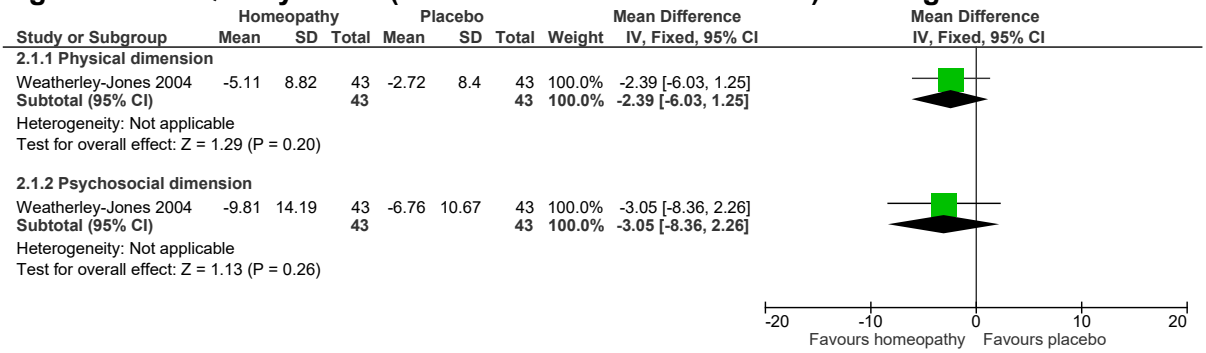


Figure 346: Fatigue (Fatigue Impact Scale) – change scores

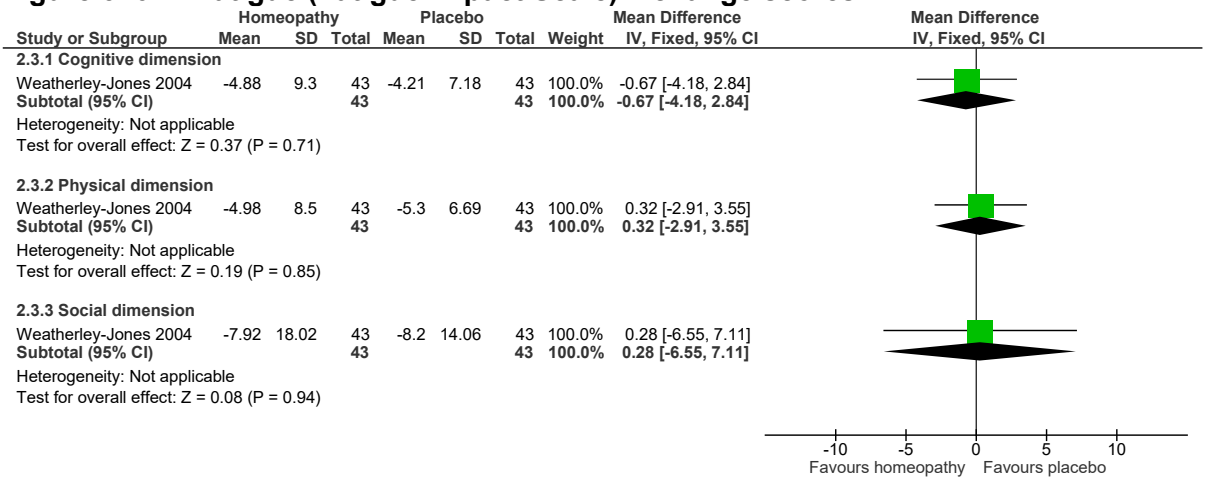


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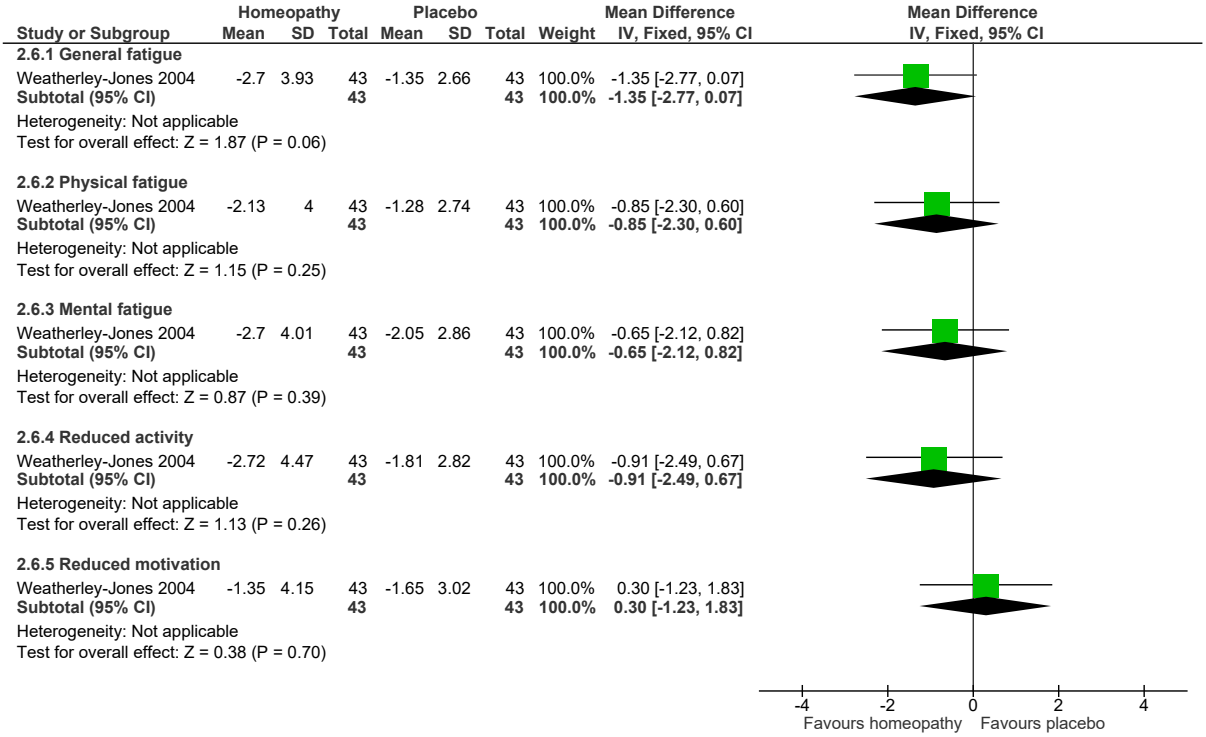
Figure 347: Fatigue (Multidimensional Fatigue Inventory sub scales) – change scores



E.4.3 Acupuncture versus Sham acupuncture: adults, severity mixed or unclear

Figure 348: Quality of life (SF12 sub scales)

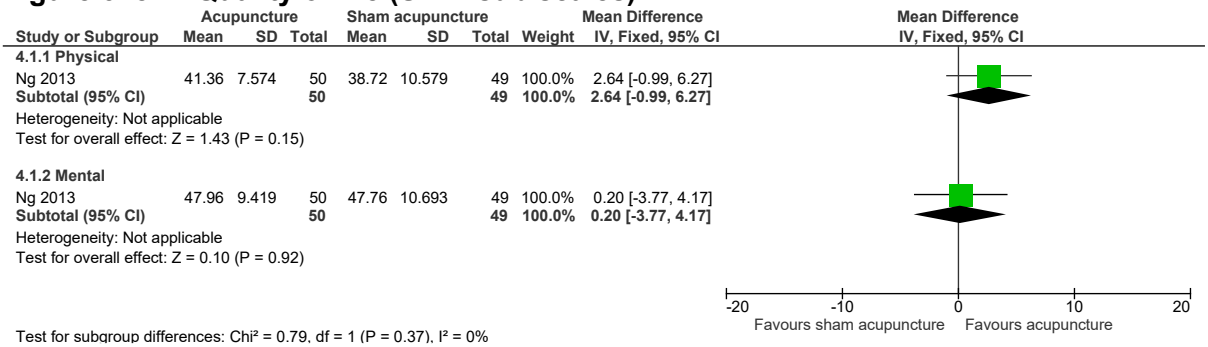


Figure 349: Fatigue (Chalder Fatigue Scale 14-item sub scales)

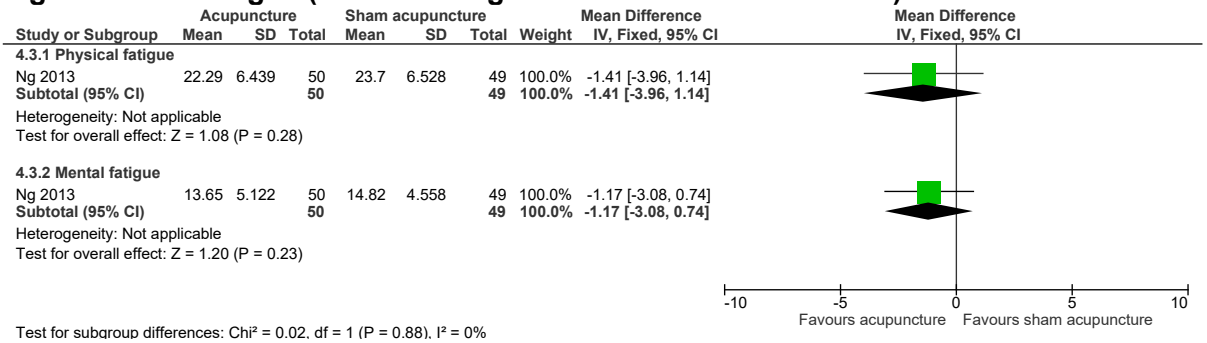


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Figure 350: Psychological status (GHQ12)

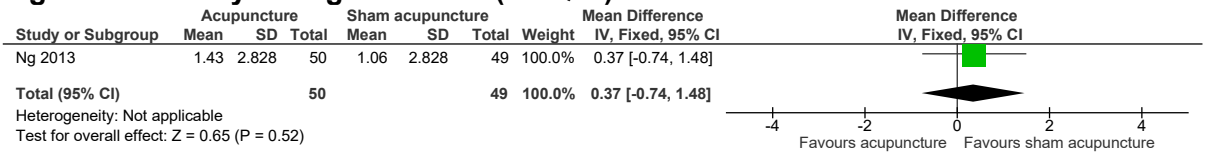
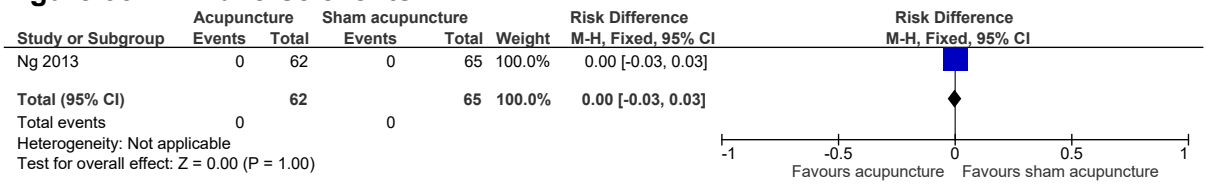


Figure 351: Adverse events



E.4.4 Abdominal tuina versus Acupuncture: adults, severity mixed or unclear

Figure 352: Fatigue (fatigue scale 14)

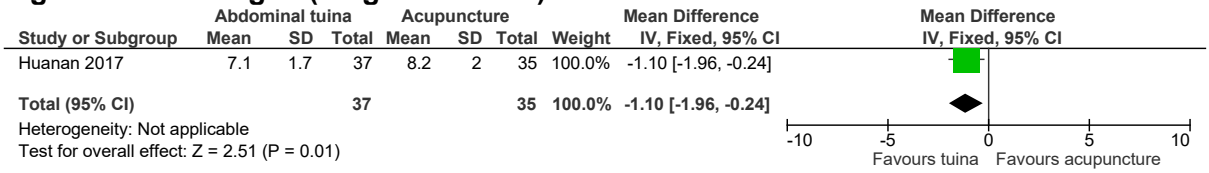


Figure 353: Psychological status (self-rating anxiety scale)

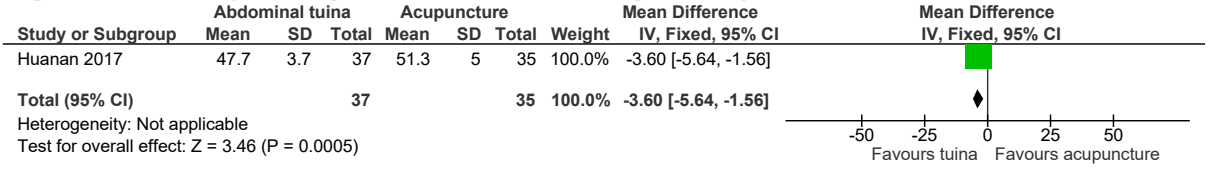


Figure 354: Psychological status (Hamilton rating scale for depression)

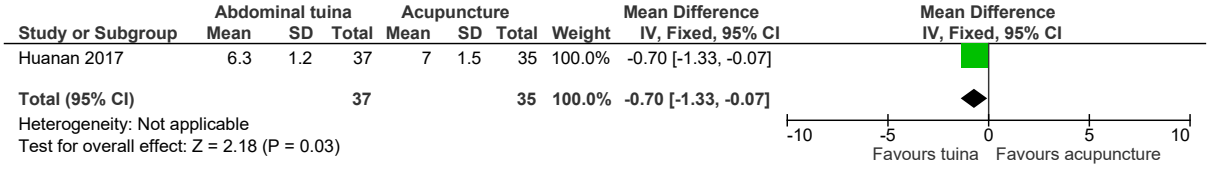


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Figure 355: Adverse events

Study or Subgroup	Abdominal tuina Events	Total	Acupuncture Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Huanan 2017	1	39	2	38	100.0%	0.49 [0.05, 5.15]
Total (95% CI)		**39**		**38**	**100.0%**	**0.49 [0.05, 5.15]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

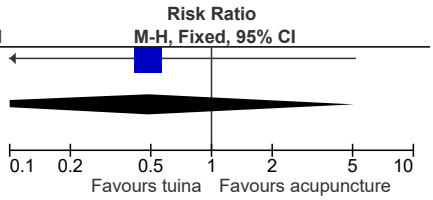
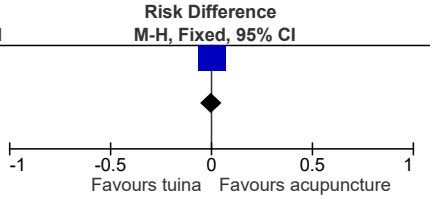


Figure 356: Serious adverse events

Study or Subgroup	Abdominal tuina Events	Total	Acupuncture Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Huanan 2017	0	39	0	38	100.0%	0.00 [-0.05, 0.05]
Total (95% CI)		**39**		**38**	**100.0%**	**0.00 [-0.05, 0.05]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



E.4.5 Myelophil versus Placebo: adults, severity mixed or unclear

Figure 357: Fatigue (numeric rating scale)

Study or Subgroup	Myelophil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Joung 2019	34.8	16.4	48	40.53	19	49	100.0%	-5.73 [-12.79, 1.33]
Total (95% CI)			**48**			**49**	**100.0%**	**-5.73 [-12.79, 1.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)

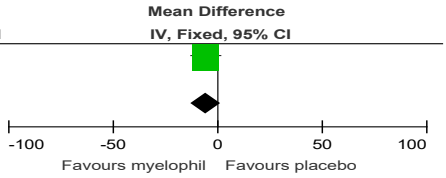


Figure 358: Fatigue (visual analogue scale change score)

Study or Subgroup	Myelophil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Joung 2019	-3	2.4	48	-2.5	2.3	49	100.0%	-0.50 [-1.44, 0.44]
Total (95% CI)			**48**			**49**	**100.0%**	**-0.50 [-1.44, 0.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

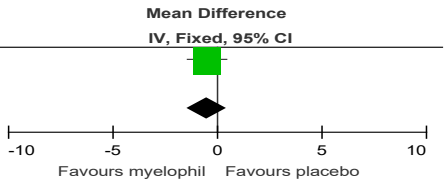


Figure 359: Fatigue (fatigue severity scale change score)

Study or Subgroup	Myelophil Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Joung 2019	-15.3	14.3	48	-11.1	11.6	49	100.0%	-4.20 [-9.39, 0.99]
Total (95% CI)			**48**			**49**	**100.0%**	**-4.20 [-9.39, 0.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)

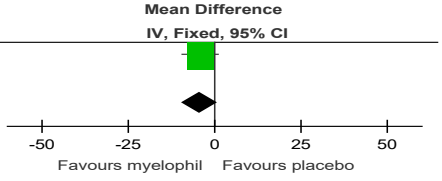


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Figure 360: Adverse events

Study or Subgroup	Myelophil Events	Myelophil Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Joung 2019	7	48	9	49	100.0%	0.79 [0.32, 1.96]
Total (95% CI)		**48**		**49**	**100.0%**	**0.79 [0.32, 1.96]**
Total events	7		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.50 (P = 0.62)

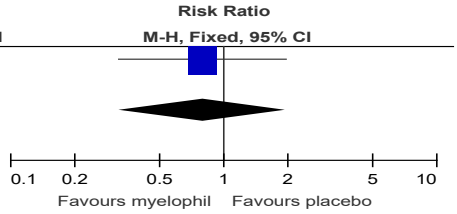
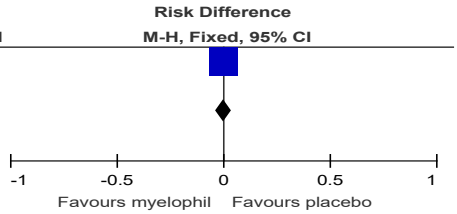


Figure 361: Adverse events (serious adverse events)

Study or Subgroup	Myelophil Events	Myelophil Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Joung 2019	0	48	0	49	100.0%	0.00 [-0.04, 0.04]
Total (95% CI)		**48**		**49**	**100.0%**	**0.00 [-0.04, 0.04]**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)



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E.5 Dietary Strategies

E.5.1 Low Sugar, Low Yeast Diet versus Healthy Eating (Advice): adults, severity mixed or unclear

Figure 362: Quality of Life (SF36 sub scales)

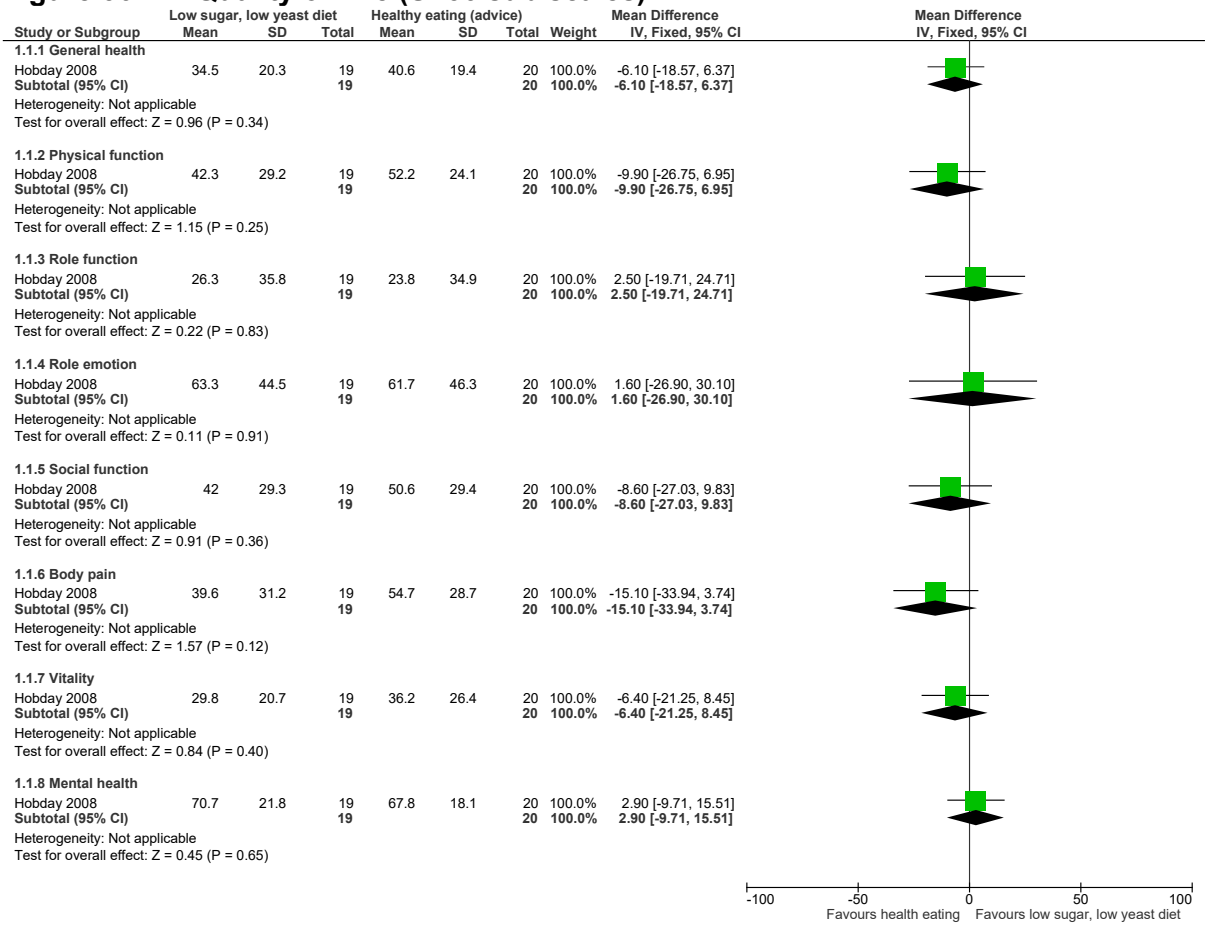

Figure 363: Fatigue (Chalder Fatigue Scale 14-item)

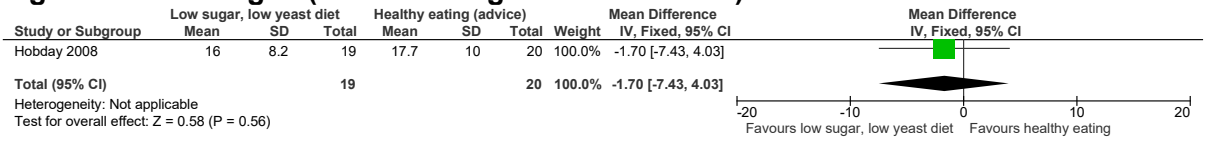

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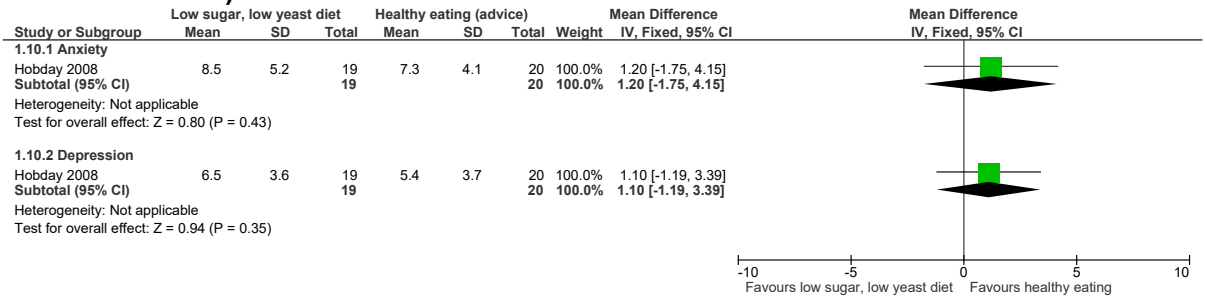
Figure 364: Psychological Status (Hospital Anxiety and Depression Scale sub scales)



E.6 Dietary Supplements

E.6.1 Acclydine and Amino Acids versus Placebo: adults, severity mixed or unclear

Figure 365: General Symptom Scales (Sickness Impact Profile-8)

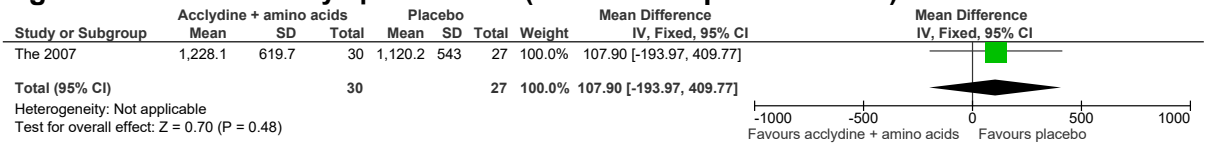


Figure 366: Fatigue (Checklist Individual Strength – Fatigue Severity sub scale)

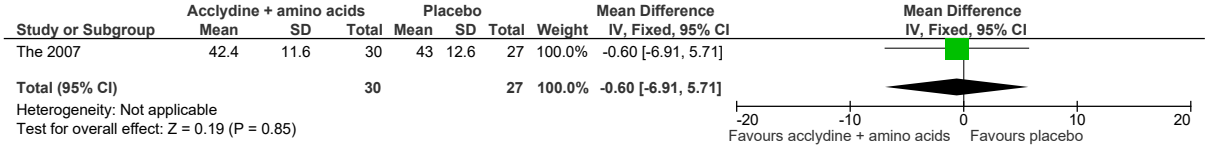


Figure 367: Activity Levels (Actometer)

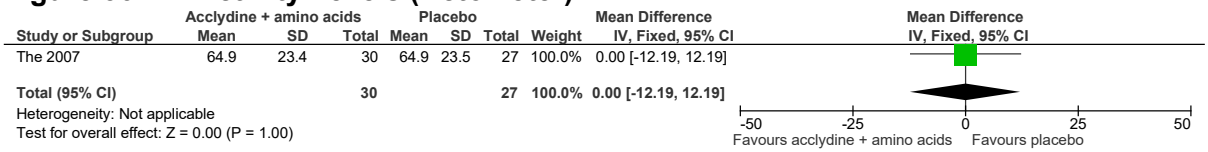
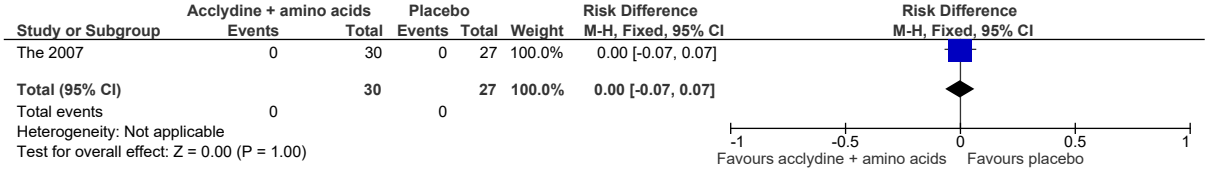


Figure 368: Adverse Events (Important Side Effects)



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E.6.2 Polynutrient supplement versus Placebo: adults, severity mixed or unclear

Figure 369: General Symptom Scales (Sickness Impact Profile-8)

Study or Subgroup	Multivitamin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Brouwers 2002	1,650	543	27	1,710	644	26	100.0%	-60.00 [-381.29, 261.29]
Total (95% CI)			**27**			**26**	**100.0%**	**-60.00 [-381.29, 261.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

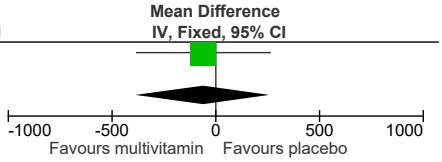


Figure 370: Fatigue (Checklist Individual Strength – Fatigue sub scale)

Study or Subgroup	Multivitamin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Brouwers 2002	48.6	7.4	27	48.2	7.6	26	100.0%	0.40 [-3.64, 4.44]
Total (95% CI)			**27**			**26**	**100.0%**	**0.40 [-3.64, 4.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)

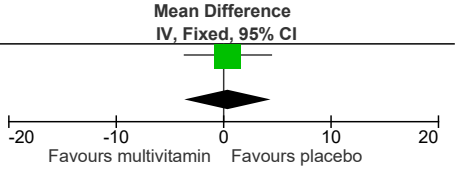
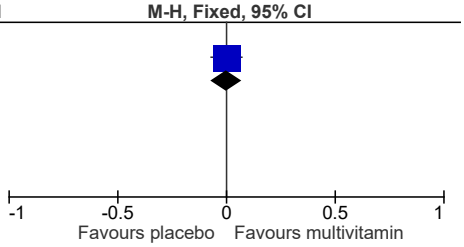


Figure 371: Quality of Life (Self-reported improvement in severity of complaints)

Study or Subgroup	Multivitamin Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
2.3.1 Completely recovered						
Brouwers 2002	0	27	0	26	100.0%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**27**		**26**	**100.0%**	**0.00 [-0.07, 0.07]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

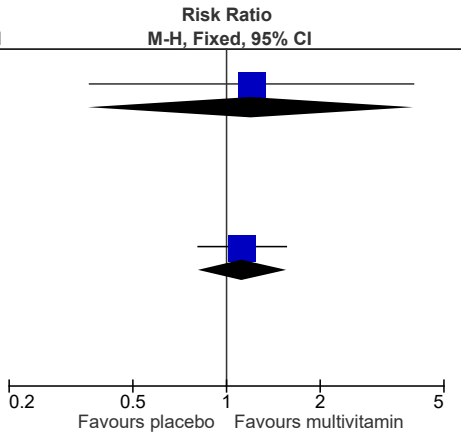


Study or Subgroup	Multivitamin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.2 Improved						
Brouwers 2002	5	27	4	26	100.0%	1.20 [0.36, 3.99]
Subtotal (95% CI)		**27**		**26**	**100.0%**	**1.20 [0.36, 3.99]**
Total events	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.76)

2.4.3 Similar						
Brouwers 2002	21	27	18	26	100.0%	1.12 [0.81, 1.56]
Subtotal (95% CI)		**27**		**26**	**100.0%**	**1.12 [0.81, 1.56]**
Total events	21		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)



Study or Subgroup	Multivitamin Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.5.4 Worse						
Brouwers 2002	1	27	0	26	100.0%	7.12 [0.14, 359.10]
Subtotal (95% CI)		**27**		**26**	**100.0%**	**7.12 [0.14, 359.10]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

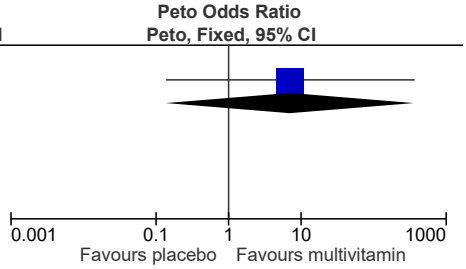


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Figure 372: Activity Levels (Actometer)

Study or Subgroup	Multivitamin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Brouwers 2002	57.2	14.6	27	65.6	22.4	26	100.0%	-8.40 [-18.62, 1.82]
Total (95% CI)			**27**			**26**	**100.0%**	**-8.40 [-18.62, 1.82]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)

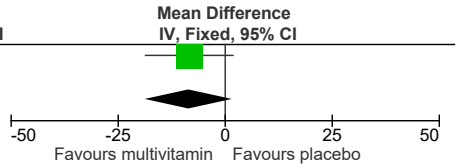
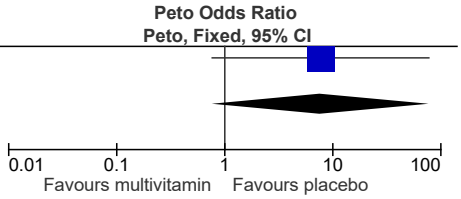


Figure 373: Adverse Events (Nausea)

Study or Subgroup	Multivitamin Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brouwers 2002	3	27	0	26	100.0%	7.70 [0.77, 77.47]
Total (95% CI)		**27**		**26**	**100.0%**	**7.70 [0.77, 77.47]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



E.6.3 Aribinoxylane versus Placebo: adults, severity mixed or unclear

Figure 374: Quality of Life (WHOQOL-BREF sub scales) - change scores

Study or Subgroup	Aribinoxylane Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.2.1 Physical wellbeing								
McDermott 2006	3.1	14.6	34	5	15.2	30	100.0%	-1.90 [-9.23, 5.43]
Subtotal (95% CI)			**34**			**30**	**100.0%**	**-1.90 [-9.23, 5.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.51 (P = 0.61)								
4.2.2 Psychological wellbeing								
McDermott 2006	1.4	9.8	34	-1	12.9	30	100.0%	2.40 [-3.27, 8.07]
Subtotal (95% CI)			**34**			**30**	**100.0%**	**2.40 [-3.27, 8.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
4.2.3 Social wellbeing								
McDermott 2006	-1.3	12.7	34	6.9	14	30	100.0%	-8.20 [-14.78, -1.62]
Subtotal (95% CI)			**34**			**30**	**100.0%**	**-8.20 [-14.78, -1.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.44 (P = 0.01)								
4.2.4 Environmental wellbeing								
McDermott 2006	-0.6	10	34	1.6	10.7	30	100.0%	-2.20 [-7.29, 2.89]
Subtotal (95% CI)			**34**			**30**	**100.0%**	**-2.20 [-7.29, 2.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.85 (P = 0.40)								

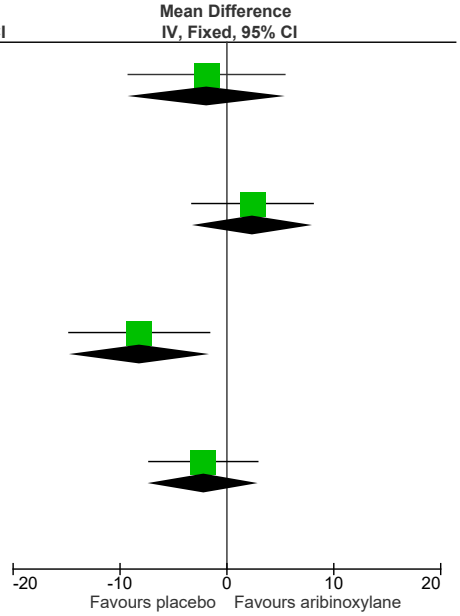


Figure 375: Quality of Life (Patient Global Impression of Change – Improvement)

Study or Subgroup	Aribinoxylane Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
McDermott 2006	4	34	4	30	100.0%	0.88 [0.24, 3.22]
Total (95% CI)		**34**		**30**	**100.0%**	**0.88 [0.24, 3.22]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)

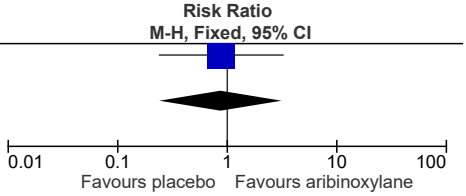


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Figure 376: Fatigue (Chalder Fatigue Scale 11-item) – change scores

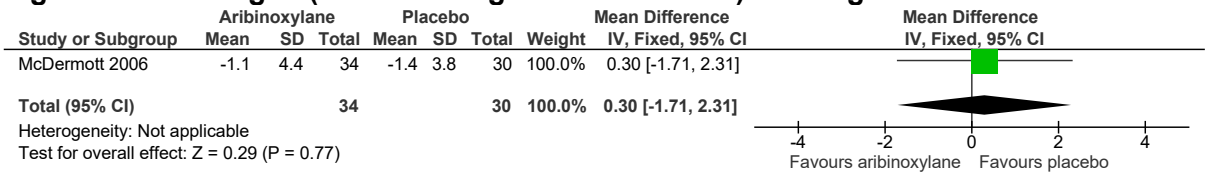


Figure 377: General Symptom Scales (Measure Yourself Medical Outcomes Profile-2) – change scores

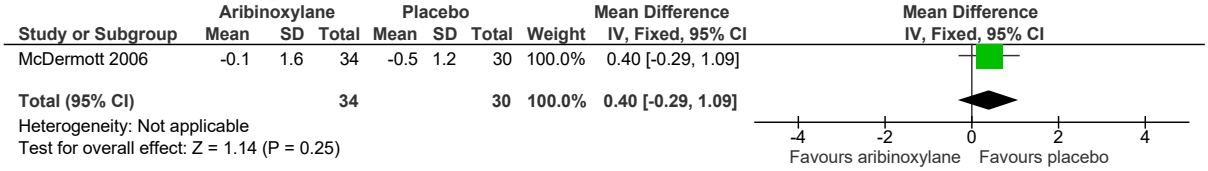


Figure 378: Psychological Status (Hospital Anxiety and Depression Scale sub scales) – change scores

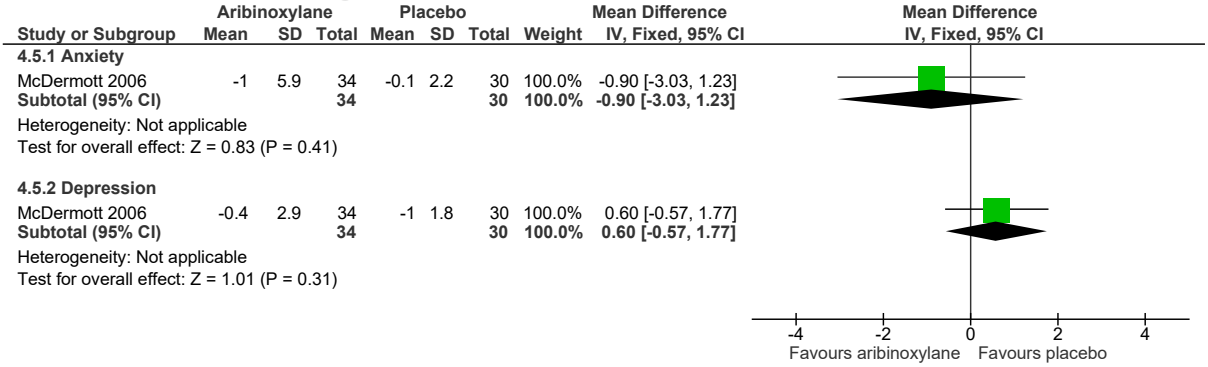
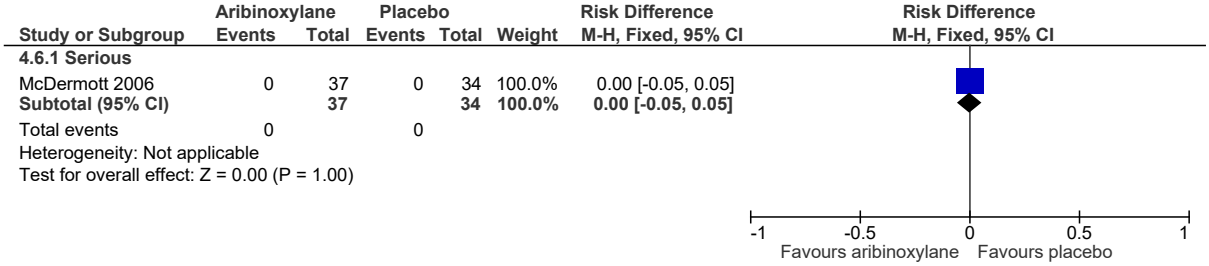


Figure 379: Adverse Events



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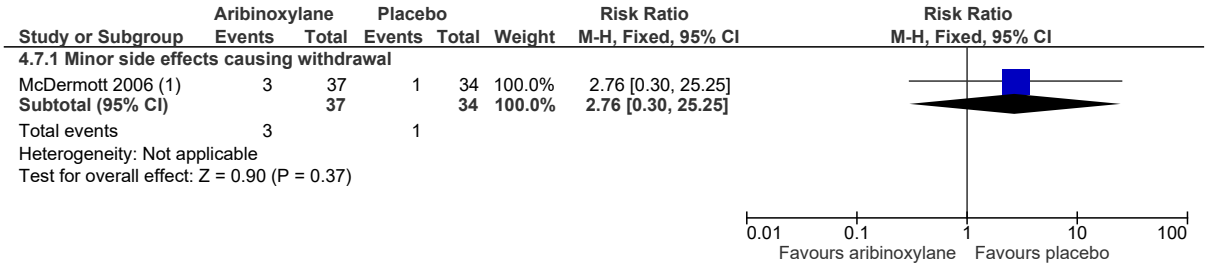


Footnotes
(1) Aribinoxylane: n=1 mild nausea; n=1 exacerbation of CFS symptoms; n=1 exacerbation of irritable bowel symptoms; Placebo: n=1...

E.6.4 Vitamin D versus Placebo: adults, severity mixed or unclear

Figure 380: Fatigue (Piper Fatigue Scale)

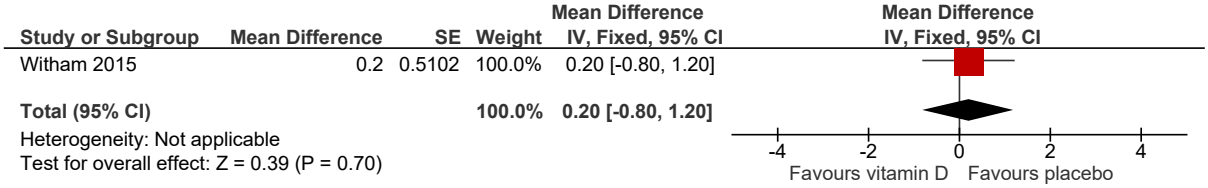


Figure 381: Psychological Status (Hospital Anxiety and Depression Scale sub scales)

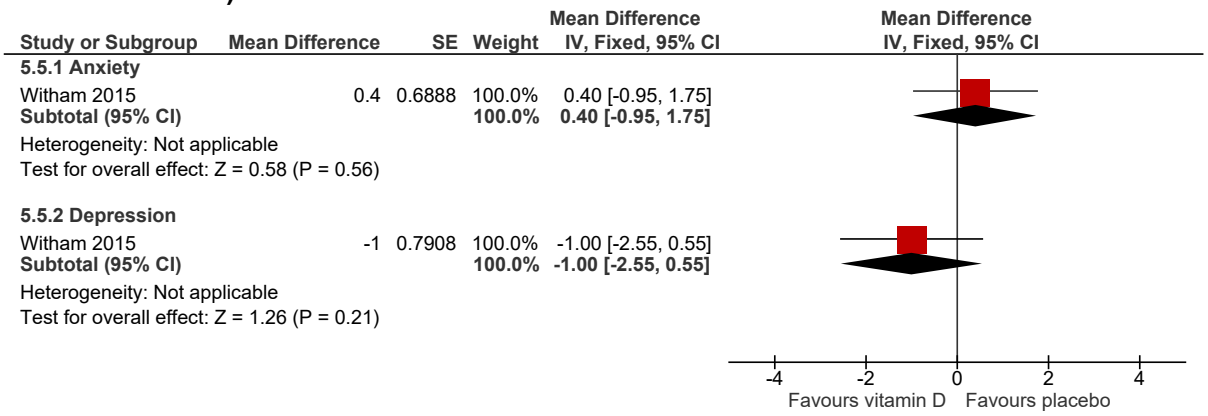
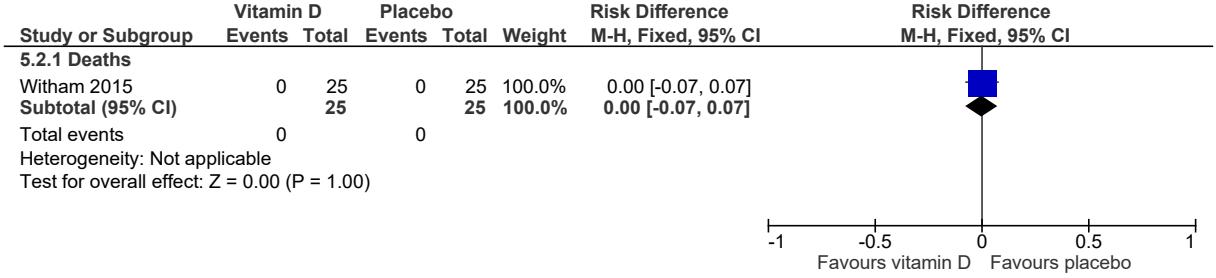


Figure 382: Adverse Events (deaths)



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E.6.5 Coenzyme Q10 and NADH versus Placebo: adults, severity mixed or unclear

Figure 383: Fatigue (Fatigue Index Scale)

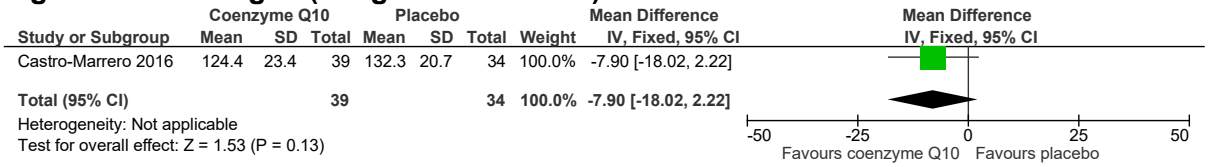

Figure 384: Pain (MgGill Pain Questionnaire sub scales)

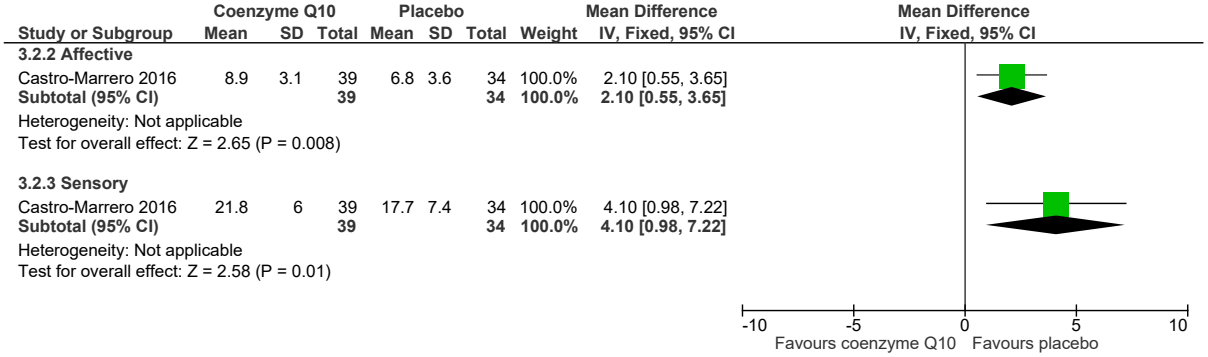

Figure 385: Sleep Quality (Global Pittsburgh Sleep Quality Index)

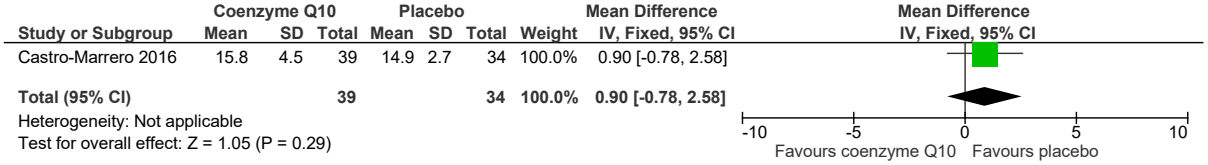

Figure 386: Adverse Events (Moderate)

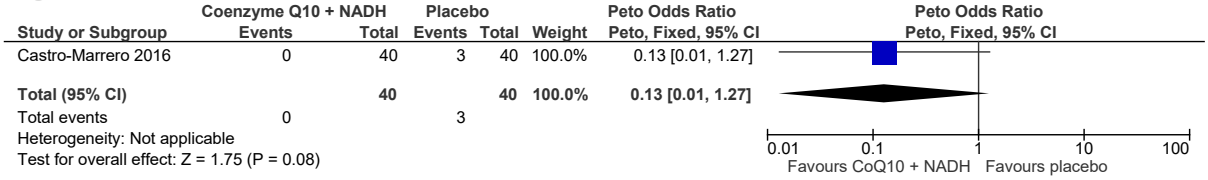

Figure 387: Exercise performance measure (VO2 max – ml/kg/min)

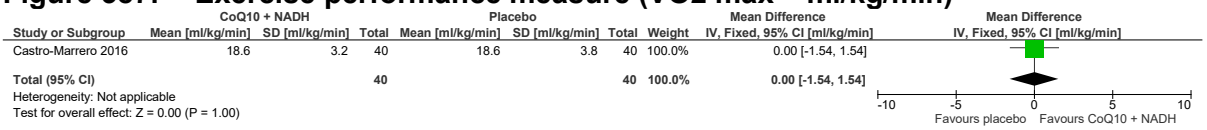

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Figure 388: Exercise performance measure (Max workload – km/h)

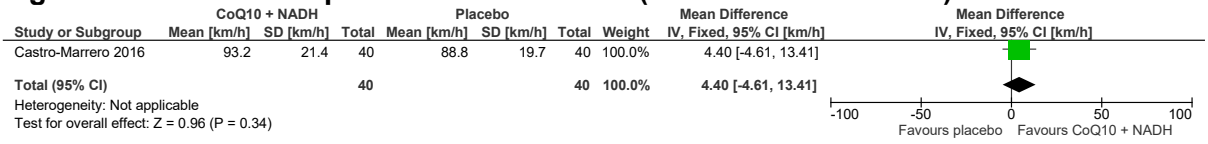
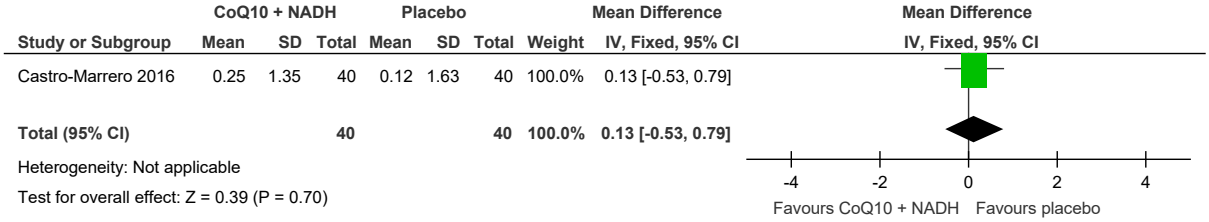


Figure 389: Exercise performance measure (Perceived exertion – Borg scale – change scores)



E.6.6 Guanidinoacetic acid (GAA) versus Placebo: adults, severity mixed or unclear

Figure 390: Quality of Life (SF36 sub scales)

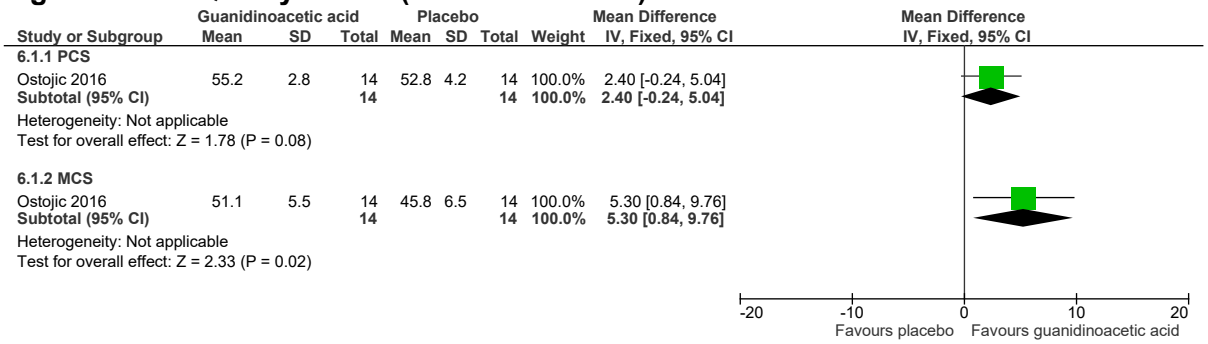


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Figure 391: Fatigue (Multidimensional Fatigue Inventory sub scales)

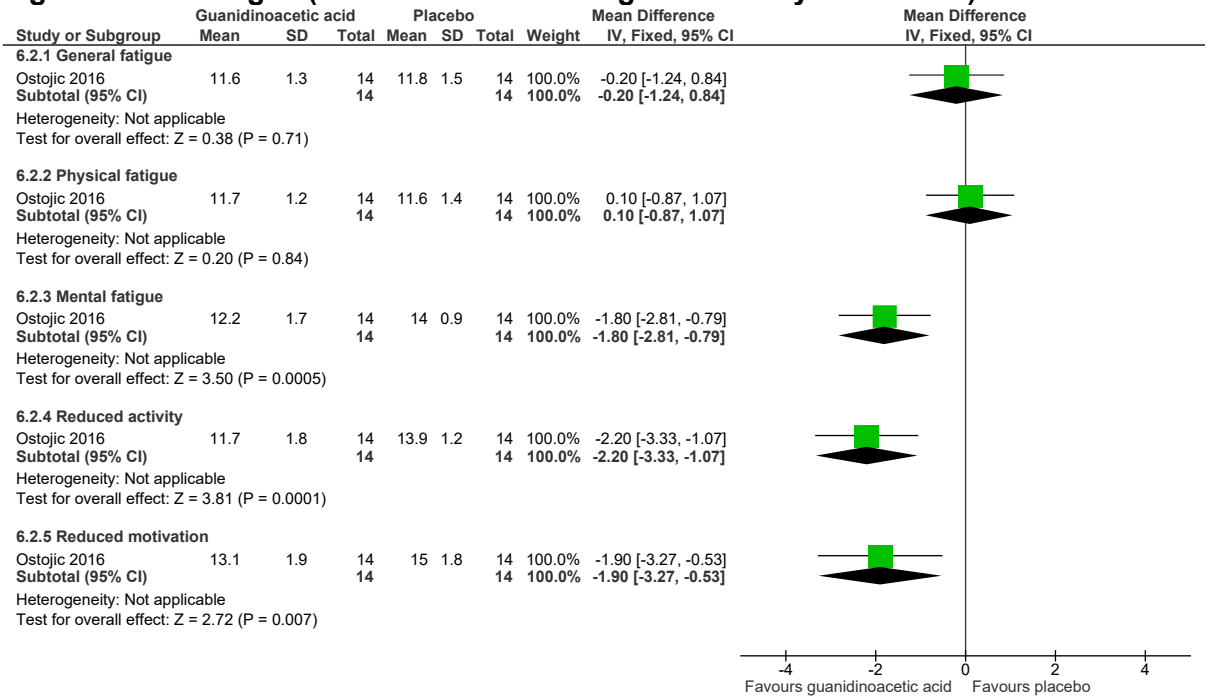


Figure 392: Pain (Visual Analogue Scale)

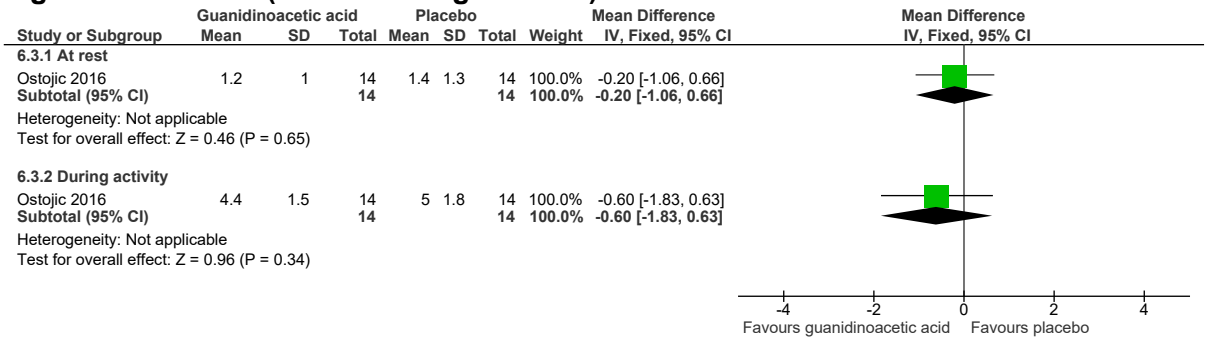
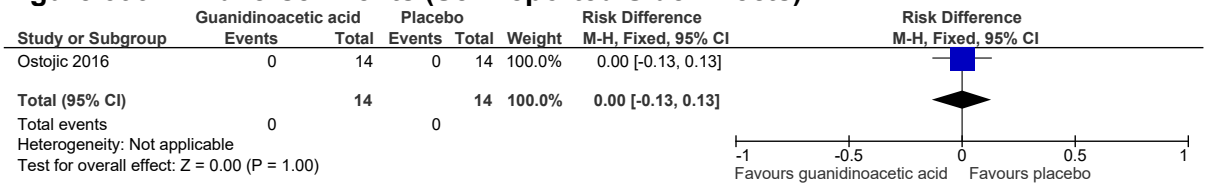


Figure 393: Adverse Events (Self-reported Side Effects)



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E.6.7 Ubiquinol-10 versus Placebo: adults, severity mixed or unclear

Figure 394: Cognitive function (Uchida-Kraepelin Psychodiagnostic Test)

Study or Subgroup	Ubiquinol-10 Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
7.1.1 Number of responses								
Fukuda 2016	222.9	74.6282	17	217.2	65.479	14	100.0%	5.70 [-43.65, 55.05]
Subtotal (95% CI)			**17**			**14**	**100.0%**	**5.70 [-43.65, 55.05]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.23 (P = 0.82)								
7.1.2 Number of correct responses								
Fukuda 2016	216	76.2775	17	211.9	66.9757	14	100.0%	4.10 [-46.35, 54.55]
Subtotal (95% CI)			**17**			**14**	**100.0%**	**4.10 [-46.35, 54.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.16 (P = 0.87)								

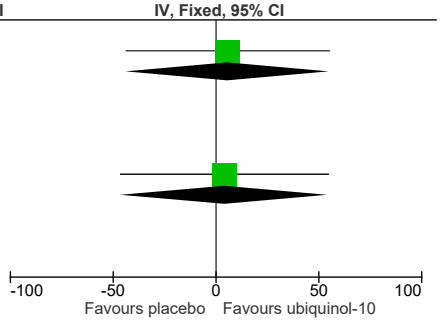
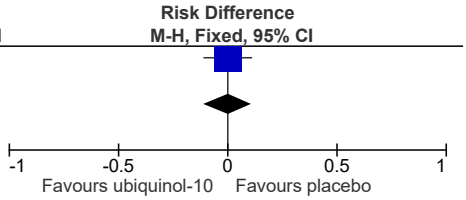


Figure 395: Adverse events (Serious)

Study or Subgroup	Ubiquinol-10 Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Fukuda 2016	0	18	0	16	100.0%	0.00 [-0.11, 0.11]
Total (95% CI)		**18**		**16**	**100.0%**	**0.00 [-0.11, 0.11]**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



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Appendix F GRADE and/or GRADE-CERQual tables

Self-management

Table 3: Clinical evidence profile: Self-management (activity pacing) versus Relaxation: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management versus Relaxation in adults	Control	Relative (95% CI)	Absolute		
Quality of life (SF36 sub scales) - Physical functioning (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 8.2 higher (5.37 lower to 21.77 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - Role physical (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 24.9 higher (1.8 lower to 51.6 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - Bodily pain (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 7.6 higher (8.61 lower to 23.81 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - General health (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12	14	-	MD 3.5 higher (11.55 lower to 18.55 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - Vitality (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12	14	-	MD 3.6 higher (7.67 lower to 14.87 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - Social functioning (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 10.3 higher (5.5 lower to 26.1 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - Role emotional (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 42.6 higher (15.77 to 69.43 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - Mental health (follow-up 5 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 11.3 higher (1.64 lower to 24.24 higher)	⊕OOO VERY LOW	CRITICAL
Physical function (Canadian Occupational Performance Measure) - Performance (follow-up 5 weeks; range of scores: 1-10; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 0.5 higher (0.62 lower to 1.62 higher)	⊕OOO VERY LOW	CRITICAL
Physical function (Canadian Occupational Performance Measure) - Satisfaction (follow-up 5 weeks; range of scores: 1-10; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	14	-	MD 1.2 higher (0.13 lower to 2.53 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 4: Clinical evidence profile: Self-management (group-based programme) versus Usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management versus Usual care in adults	Control	Relative (95% CI)	Absolute		
Quality of life (SF36) - Mental component (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	59	-	MD 1.4 lower (4.93 lower to 2.13 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF36) - Physical component (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58	59	-	MD 0.5 higher (2.49 lower to 3.49 higher)	⊕⊕⊕O MODERATE	CRITICAL
Fatigue (Fatigue Severity Scale) (follow-up 12 months; range of scores: 9-63; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	59	59	-	MD 0.7 lower (3.15 lower to 1.75 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 5: Clinical evidence profile: Self-management (Adaptive pacing therapy) versus Usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adaptive pacing therapy	Usual care	Relative (95% CI)	Absolute		
Quality of life (EQ5D) (follow-up 52 weeks; range of scores: -0.594-1; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	148	151	-	MD 0.01 higher (0.06 lower to 0.08 higher)	⊕⊕OO LOW	CRITICAL
General symptom scales (proportion with positive change (very much better or much better) (follow-up mean 134 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	45/118 (38.1%)	41.7%	OR 0.8 (0.4 to 1.6)	53 fewer per 1000 (from 195 fewer to 117 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder fatigue scale) (follow-up mean 134 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	120	115	-	MD 0.3 higher (1.7 lower to 2.3 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical function) (follow-up mean 134 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	118	115	-	MD 3.6 lower (9.6 lower to 2.4 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS anxiety) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	149	149	-	MD 0.7 lower (1.46 lower to 0.06 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS depression) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	149	151	-	MD 0.6 lower (1.34 lower to 0.14 higher)	⊕⊕OO LOW	CRITICAL
Pain (numeric rating scale) - muscle pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	151	149	-	MD 0.04 lower (0.35 lower to 0.27 higher)	⊕OOO VERY LOW	CRITICAL
Pain (numeric rating scale) - joint pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	149	151	-	MD 0.1 higher (0.24 lower to 0.44 higher)	⊕OOO VERY LOW	CRITICAL

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Sleep quality (Jenkins sleep scale) (follow-up 52 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	150	151	-	MD 0.1 lower (0.75 lower to 0.55 higher)	⊕⊕OO LOW	CRITICAL
Return to work (Work and social adjustment scale) (follow-up mean 134 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	120	115	-	MD 1.3 higher (1.2 lower to 3.8 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (adverse reactions) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/159 (1.3%)	1.3%	RR 1.01 (0.14 to 7.06)	0 more per 1000 (from 11 fewer to 79 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (non-serious) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	no serious imprecision	none	152/159 (95.6%)	93.1%	RR 1.03 (0.97 to 1.08)	28 more per 1000 (from 28 fewer to 74 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	serious[3]	none	15/159 (9.4%)	4.4%	RR 2.16 (0.9 to 5.15)	51 more per 1000 (from 4 fewer to 183 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk test) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	111	118	-	MD 5.7 lower (24.44 lower to 13.04 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is <95% [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 increment because the majority of the evidence included an indirect outcome (adverse events not necessarily treatment-related).

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Table 6: Clinical evidence profile: Self-management programme (delivered by booklet/CDs with step counter or actigraphy) versus Usual care: adults – severe

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management	Usual care	Relative (95% CI)	Absolute		
Fatigue (fatigue severity scale) (follow-up 12 months; range of scores: 9-63; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	78	46	-	MD 0.37 lower (0.66 to 0.08 lower)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical function) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	80	45	-	MD 2.06 higher (6.45 lower to 10.57 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	80	45	-	MD 4.89 lower (8.3 to 1.48 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck anxiety inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	78	43	-	MD 2.5 lower (6.34 lower to 1.34 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by one increment): CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is <95% [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 7: Clinical evidence profile: Self-management (activity pacing) versus Stairway to health programme (structured incremental rehab programme): children/young people, severe

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management versus Stairway to health programme in children/young people	Control	Relative (95% CI)	Absolute		
Quality of life (Child Health Questionnaire) (follow-up 12 months; range of scores: 1-5; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	5	6	-	MD 2 higher (1.18 to 2.82 higher)	⊕⊕OO LOW	CRITICAL
General symptom scales (Young person functional ability scale) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5	6	-	MD 12.75 lower (40.3 lower to 14.8 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder fatigue scale) (follow-up 12 months; range of scores: 0-42; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5	6	-	MD 4 higher (5.56 lower to 13.56 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Birleson depression scale) (follow-up 12 months; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5	6	-	MD 1.93 higher (5.02 lower to 8.88 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale - anxiety) (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5	6	-	MD 0.6 higher (4.46 lower to 5.66 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (% school attendance) (follow-up 18 months; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	5	6	-	MD 55.9 lower (98.14 to 13.66 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Psychological/behavioural interventions

Cognitive behavioural therapy

Table 8: Clinical evidence profile: CBT versus usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT versus no treatment/wait list control/usual care**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (EQ5D) - individual face-to-face CBT (follow-up 52 weeks; range of scores: -0.594-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	143	151	-	MD 0.1 higher (0.03 to 0.17 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-36 mental score - group based CBT (follow-up 6-12 months; measured with: SF-36 mental score. Pooled 6 and 12 months data.; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	51	-	MD 4.35 higher (0.72 to 7.98 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-36 physical score - group based CBT (follow-up 6-12 months; measured with: SF-36 physical score. Pooled 6 and 12 months data.; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]i	none	52	51	-	MD 1.63 lower (4.05 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL

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Quality of life: Health status - group based CBT (follow-up 6-12 months; measured with: Health status (HUI3). Pooled 6 and 12 month data.; range of scores: -0.36-1; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	51	-	MD 0.03 higher (0.05 lower to 0.11 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales: Clinical Global Impression Scale - individual face-to-face CBT (follow-up mean 134 weeks; assessed with: Proportion with change (very much better or much better))												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	50/119 (42%)	41.7%	OR 0.9 (0.5 to 1.62)	25 fewer per 1000 (from 154 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
General symptom scales: sickness Impact profile 8 - web/written CBT (follow-up 6-12 months; range of scores: 0-5799; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency[4]	serious[2]	serious[3]	none	244	165	-	MD 409.81 lower (531.36 to 288.25 lower)	⊕OOO VERY LOW	CRITICAL
General symptom scales: sickness Impact profile 8 - group-based CBT (follow-up 6-12 months; range of scores: 0-5799; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency[4]	serious[2]	no serious imprecision	none	136	68	-	MD 589 lower (762.88 to 415.12 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue (fatigue severity 0-10 scale) - change scores - face-to-face CBT (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	30	30	-	MD 1.9 lower (3.3 to 0.5 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Checklist Individual strength - fatigue severity) - web/written CBT (follow-up 6-12 months; range of scores: 8-56; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	299	221	-	MD 7.19 lower (9.13 to 5.25 lower)	⊕⊕OO LOW	CRITICAL
Fatigue/fatigability (Checklist Individual strength - fatigue severity) - group-based CBT (follow-up 6-12 months; range of scores: 8-56; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	136	68	-	MD 13.1 lower (16.15 to 10.05 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder Fatigue Questionnaire) - web/written CBT (follow-up mean 6 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	152	76	-	MD 3.69 lower (5.77 to 1.61 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder Fatigue Questionnaire) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 month data; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	51	-	MD 2.61 lower (4.92 to 0.3 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder fatigue questionnaire) - individual face-to-face CBT (follow-up 134 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	115	-	MD 1.4 lower (3.4 lower to 0.6 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning sub-scale) - web/written CBT (follow-up 6-12 months; range of scores: 0-100; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	299	221	-	MD 6.25 higher (2.58 to 9.92 higher)	⊕⊕OO LOW	CRITICAL
Physical functioning (SF36 physical functioning sub-scale) - group-based CBT (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	136	68	-	MD 11.1 higher (4.87 to 17.33 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF-36 physical functioning sub-scale) - individual face-to-face CBT (follow-up mean 134 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	115	-	MD 2.8 higher (3.2 lower to 8.8 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (total words recalled) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	51	-	MD 0.69 higher (0.47 lower to 1.85 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (correct words) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	51	-	MD 0.8 higher (0.3 lower to 1.9 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (reaction time) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	51	-	MD 0.93 higher (0.86 to 1 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Symptom Checklist 90 - psychological distress) - web/written CBT (follow-up 6 months; range of scores: 90-450; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	160	80	-	MD 17.1 lower (29.31 to 4.89 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Symptom Checklist 90 - psychological distress) - group-based CBT (follow-up 6 months; range of scores: 90-450; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	136	68	-	MD 18 lower (28.61 to 7.39 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Brief Symptom Inventory - psychological distress) - change scores - web/written CBT (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[5]	no serious imprecision	none	52	52	-	MD 0.1 lower (0.2 lower to 0 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS anxiety) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	51	-	MD 1.27 lower (2.52 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS anxiety) - individual face-to-face CBT (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												

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2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	173	179	-	MD 1.25 lower (1.95 to 0.55 lower)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS depression) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	51	-	MD 0.56 lower (1.69 lower to 0.57 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS depression) - individual face-to-face CBT (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	173	179	-	MD 1.47 lower (2.17 to 0.76 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (General health questionnaire) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	51	-	MD 2.21 lower (4.52 lower to 0.1 higher)	⊕OOO VERY LOW	CRITICAL
Pain (joint pain numeric rating scale) - individual face-to-face CBT (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	151	-	MD 0.25 lower (0.58 lower to 0.08 higher)	⊕OOO VERY LOW	CRITICAL
Pain (muscle pain numeric rating scale) - individual face-to-face CBT (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	145	149	-	MD 0.38 lower (0.69 to 0.07 lower)	⊕OOO VERY LOW	CRITICAL
Sleep quality (Jenkins sleep scale) - individual face-to-face CBT (follow-up 52 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	151	-	MD 1.1 lower (2.04 to 0.16 lower)	⊕⊕OO LOW	CRITICAL
Adverse events (self-reported) - web/written CBT (follow-up 6 months; assessed with: Fatigue, pain, distress, other)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11/77 (14.3%)	26.1%	RR 0.55 (0.26 to 1.14)	117 fewer per 1000 (from 193 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (non-serious) - individual face-to-face CBT (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,6]	no serious imprecision	none	143/161 (88.8%)	93.1%	RR 0.95 (0.89 to 1.02)	47 fewer per 1000 (from 102 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious) - individual face-to-face CBT (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,6]	very serious[3]	none	7/161 (4.3%)	4.4%	RR 0.99 (0.36 to 2.77)	0 fewer per 1000 (from 28 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (adverse reactions) - individual face-to-face CBT (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/161 (1.9%)	1.3%	RR 1.49 (0.25 to 8.8)	6 more per 1000 (from 10 fewer to 101 more)	⊕OOO VERY LOW	CRITICAL
Activity levels (Actigraphy mean score) - web/written CBT (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	127	60	-	MD 9.8 higher (3.21 to 16.39 higher)	⊕OOO VERY LOW	CRITICAL
Activity levels (Number of days in bed per week) - change scores - individual face-to-face CBT (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	30	30	-	MD 2.8 lower (4 to 1.6 lower)	⊕OOO VERY LOW	CRITICAL
Activity levels (Percentage interference with activities) - change scores - individual face-to-face CBT (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	30	30	-	MD 14 lower (25 to 3 lower)	⊕OOO VERY LOW	CRITICAL

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Return to school or work (Work and Social Adjustment Scale) - web/written CBT (follow-up 6 months; range of scores: 0-40; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	73	75	-	MD 5 lower (7.62 to 2.38 lower)	⊕OOO VERY LOW	CRITICAL
Return to school or work (Work and social adjustment scale) - individual face-to-face CBT (follow-up mean 134 weeks; range of scores: 0-40; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	115	-	MD 1.1 lower (3.6 lower to 1.4 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Normal walking speed) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	51	-	MD 2.83 higher (1.12 to 4.54 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Shuttles walked) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	51	-	MD 1.2 higher (0.99 to 1.41 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 min walk test) - individual face-to-face CBT (follow-up 12 months; Better indicated by higher values)											
2	randomised trials	very serious[1]	serious[4]	serious[2]	no serious imprecision	none	153	148	-	MD 8.87 higher (7.41 lower to 25.15 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-10; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	51	-	MD 0.98 higher (0.87 to 1.09 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC or Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear (Sharpe 1996, O'Dowd 2006, Wiborg 2015, Knoop 2008, Tummers 2012) or <95% (PACE trial, Janse 2018) [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
[5] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments): 1. 1994 CDC or Oxford criteria used;

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PEM is not a compulsory feature [original analysis]; percentage of participants with PEM unclear [PEM reanalysis]; 2. Not all patients turned out to have ME/CFS (Tummers 2012).
[6] Downgraded by 1 increment because the majority of the evidence included an indirect outcome (adverse events not necessarily treatment-related).

Table 9: Clinical evidence profile: Group-based cognitive behavioural stress management versus psychoeducation: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group-based cognitive behavioural stress management versus control (psycho-education)	Control	Relative (95% CI)	Absolute		
Quality of life: QOLI (follow-up 12 weeks; measured with: Quality of Life Inventory (QOLI) raw score; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	38	20	-	MD 0.35 higher (0.49 lower to 1.19 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (follow-up 12 weeks; measured with: CDC Symptom Inventory; range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	38	20	-	MD 0.07 lower (0.27 lower to 0.13 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Profile of Mood States - total mood disturbance @ 12 weeks) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	38	20	-	MD 6.68 higher (7.8 lower to 21.16 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Perceived Stress Scale) (follow-up 12 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	38	20	-	MD 3.65 higher (0.7 lower to 8 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of

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participants with PEM unclear – inadequate description of 'unusual fatigue after exertion' to confirm if patients had PEM [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 10: Clinical evidence profile: CBT (group-based) versus education and support group: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT (group-based) versus education and support group	Control	Relative (95% CI)	Absolute		
Quality of life (SF36 mental) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	50	-	MD 3.16 higher (0.05 lower to 6.37 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 physical) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 0.4 lower (2.86 lower to 2.06 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (Health status (HUI3)) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: -0.36-1; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 0.02 higher (0.01 lower to 0.05 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder fatigue score) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	50	-	MD 3.16 lower (5.59 to 0.73 lower)	⊕OOO VERY LOW	CRITICAL
Cognitive function (total words recalled) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	50	-	MD 0.77 higher (0.32 lower to 1.86 higher)	⊕OOO VERY LOW	CRITICAL

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Cognitive function (correct words) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	50	-	MD 0.84 higher (0.26 lower to 1.94 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (reaction time) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 0.99 higher (0.9 to 1.08 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS anxiety) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 0.51 lower (1.7 lower to 0.68 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS depression) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 0.13 lower (1.13 lower to 0.87 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (General health Questionnaire) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52	50	-	MD 1.8 lower (4.17 lower to 0.57 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Normal walking speed) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 1.77 higher (0.03 to 3.51 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Shuttles walked) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 1.16 higher (0.94 to 1.38 higher)	⊕OOO VERY LOW	CRITICAL

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Exercise performance measure (Perceived fatigue - modified Borg scale) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52	50	-	MD 1 higher (0.86 to 1.14 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 11: Clinical evidence profile: CBT (individual face-to-face) versus multidisciplinary rehabilitation: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face) versus multidisciplinary rehabilitation**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life: SF-36 mental component summary (follow-up 12 months; measured with: SF36 mental component summary; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	60	62	-	MD 1.59 lower (5.14 lower to 1.96 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-36 physical component summary (follow-up 12 months; measured with: SF36 physical component summary; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	60	62	-	MD 2.67 lower (6.79 lower to 1.45 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (Sickness Impact Profile 8) (follow-up 12 months; range of scores: 0-6160; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	60	62	-	MD 50.78 lower (288.24 lower to 186.68 higher)	⊕⊕OO LOW	CRITICAL

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Fatigue (Checklist Individual Strength - fatigue severity) (follow-up 12 months; range of scores: 8-56; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	60	62	-	MD 5.69 higher (0.76 to 10.62 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Symptom Checklist-90) (follow-up 12 months; range of scores: 90-450; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	60	62	-	MD 7.83 higher (4.19 to 11.47 higher)	⊕⊕OO LOW	CRITICAL
Activity levels (Accelerometer) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	60	62	-	MD 2009.58 higher (19140.04 lower to 23159.2 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 12: Clinical evidence profile: CBT (individual face-to-face) versus relaxation: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT versus relaxation techniques (i.e. Alexander technique)**	**Control**	**Relative (95% CI)**	**Absolute**		
General symptom scales (self-rating of much/very much better) (follow-up mean 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17/25 (68%)	35.7%	RR 1.9 (1.08 to 3.35)	321 more per 1000 (from 29 more to 839 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder Fatigue questionnaire) (follow-up 6 months; range of scores: 0-11; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	26	-	MD 3.1 lower (5.25 to 0.95 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue problem rating) (follow-up 6 months; range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	27	26	-	MD 2.1 lower (3.21 to 0.99 lower)	⊕OOO VERY LOW	CRITICAL
Physical functioning (short form general health survey physical functioning scale (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	27	26	-	MD 33.2 higher (18.42 to 47.98 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 6 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	26	-	MD 2.2 lower (6.38 lower to 1.98 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (General health questionnaire) (follow-up 6 months; range of scores: 0-12; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	26	-	MD 0.9 lower (2.95 lower to 1.15 higher)	⊕OOO VERY LOW	CRITICAL
Return to school or work (Full or part time employment) (follow-up 5 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14/25 (56%)	39.3%	RR 1.43 (0.8 to 2.54)	169 more per 1000 (from 79 fewer to 605 more)	⊕OOO VERY LOW	CRITICAL
Return to school or work (Work and social adjustment scale) (follow-up 6 months; range of scores: 0-8; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	27	26	-	MD 2.1 lower (3.18 to 1.02 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1991 CDC (Schluederberg 1992)/1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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Table 13: Clinical evidence profile: CBT (individual face-to-face) versus adaptive pacing therapy: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT (individual face-to-face) versus adaptive pacing therapy	Control	Relative (95% CI)	Absolute		
Quality of life (EQ5D) (follow-up 52 weeks; range of scores: -0.594-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	143	148	-	MD 0.09 higher (0.02 to 0.16 higher)	⊕OOO VERY LOW	CRITICAL
General symptoms scales: Clinical Global Impression scale (follow-up mean 134 weeks; assessed with: Clinical Global Impression scale change: very much better or much better)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	50/119 (42%)	38.1%	OR 1.2 (0.7 to 2.06)	44 more per 1000 (from 80 fewer to 178 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder fatigue questionnaire) (follow-up mean 134 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	120	-	MD 1.6 lower (3.6 lower to 0.4 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF-36 physical functioning sub-scale) (follow-up mean 134 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	118	-	MD 6.4 higher (0.4 to 12.4 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS anxiety scale) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	149	-	MD 0.7 lower (1.45 lower to 0.05 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS depression scale) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	149	-	MD 0.8 lower (1.56 to 0.04 lower)	⊕⊕OO LOW	CRITICAL
Pain (muscle pain numeric rating scale) (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	145	151	-	MD 0.34 lower (0.65 to 0.03 lower)	⊕OOO VERY LOW	CRITICAL
Pain (joint pain numeric rating scale) (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	149	-	MD 0.35 lower (0.68 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL
Sleep quality (Jenkins sleep scale) (follow-up 52 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	150	-	MD 0.9 lower (1.79 to 0.01 lower)	⊕⊕OO LOW	CRITICAL
Adverse events (non-serious AEs) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	no serious imprecision	none	143/161 (88.8%)	95.6%	RR 0.93 (0.87 to 0.99)	67 fewer per 1000 (from 10 fewer to 124 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious AEs) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	serious[3]	none	7/161 (4.3%)	9.4%	RR 0.46 (0.19 to 1.1)	51 fewer per 1000 (from 76 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (adverse reactions) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/161 (1.9%)	1.3%	RR 1.48 (0.25 to 8.75)	6 more per 1000 (from 10 fewer to 101 more)	⊕OOO VERY LOW	CRITICAL
Return to school/work (Work and Social Adjustment Scale) (follow-up mean 134 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	150	143	-	MD 2.4 lower (4.8 lower to 0 higher)	⊕OOO VERY LOW	CRITICAL

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Exercise performance measure (6 min walk test) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	123	111	-	MD 4.2 higher (13.99 lower to 22.39 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is <95% [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 increment because the majority of the evidence included an indirect outcome (AEs not necessarily treatment-related)

Table 14: Clinical evidence profile: CBT (individual face-to-face) versus GET: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face) versus GET**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (EQ5D) (follow-up 52 weeks; range of scores: -0.594-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	143	-	MD 0.04 higher (0.03 lower to 0.11 higher)	⊕⊕OO LOW	CRITICAL
General symptom scales (Clinical global impression scale - positive change (very much or much better)) (follow-up 134 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	50/119 (42%)	48%	RR 0.87 (0.66 to 1.16)	62 fewer per 1000 (from 163 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 134 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	127	-	MD 0.7 lower (2.75 lower to 1.35 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning sub-scale) (follow-up 134 weeks; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	119	127	-	MD 2.4 higher (4.45 lower to 9.25 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (HADS anxiety) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	144	-	MD 0.3 lower (1.25 lower to 0.65 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS depression) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	144	-	MD 0.1 higher (0.75 lower to 0.95 higher)	⊕⊕OO LOW	CRITICAL
Pain (numeric rating scale) - muscle pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	145	144	-	MD 0.04 higher (0.27 lower to 0.35 higher)	⊕OOO VERY LOW	CRITICAL
Pain (numeric rating scale) - joint pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	144	-	MD 0.01 higher (0.3 lower to 0.32 higher)	⊕OOO VERY LOW	CRITICAL
Sleep quality (Jenkins sleep scale) (follow-up 52 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	144	-	MD 0.9 higher (0.21 lower to 2.01 higher)	⊕⊕OO LOW	CRITICAL
Adverse events (non-serious) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	no serious imprecision	none	143/161 (88.8%)	93.1%	RR 0.95 (0.89 to 1.02)	47 fewer per 1000 (from 102 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	serious[3]	none	7/161 (4.3%)	8.1%	RR 0.54 (0.22 to 1.31)	37 fewer per 1000 (from 63 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL

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Adverse events (adverse reactions) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/161 (1.9%)	1.3%	RR 1.49 (0.25 to 8.8)	6 more per 1000 (from 10 fewer to 101 more)	⊕OOO VERY LOW	CRITICAL
Return to school/work (Work and social adjustment scale) (follow-up 134 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	119	126	-	MD 0.3 higher (2.33 lower to 2.93 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk test) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	123	110	-	MD 25 lower (47.54 to 2.46 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] Downgraded by 1 increment because the majority of the evidence included an indirect outcome (AEs not necessarily treatment-related)

Table 15: Clinical evidence profile: CBT (group-based) + GET versus usual care/exercise counselling: age and severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT + GET (group-based) versus usual care**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF36 emotional role) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 10.76 lower (27.42 lower to 5.9 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 general health) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	58	57	-	MD 0.43 higher (5.45 lower to 6.31 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (SF36 physical role) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 5.43 lower (13.4 lower to 2.54 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 social function) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 6.8 lower (16.16 lower to 2.56 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 vitality) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 3.66 lower (9.36 lower to 2.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 physical functioning) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 5.65 lower (13.92 lower to 2.62 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 mental health) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 4.61 lower (12.31 lower to 3.09 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 bodily pain) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 7.53 lower (15.39 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (follow-up 12 months; measured with: Stanford Health Assessment Questionnaire - global health status; range of scores: 0-10; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 0.44 higher (0.29 lower to 1.17 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (Stanford Health Assessment Questionnaire) (follow-up 12 months; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 0.13 higher (0.12 lower to 0.38 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Stanford Health Assessment Questionnaire - pain intensity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	58	57	-	MD 0.63 higher (0.23 lower to 1.49 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 16: Clinical evidence profile: CBT (individual face-to-face) versus counselling: age and severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face)**	**Counselling**	**Relative (95% CI)**	**Absolute**		
Fatigue (Chalder fatigue scale) (follow-up 6 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	20	-	MD 2.2 higher (3.7 lower to 8.1 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale - anxiety) (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	20	-	MD 1.8 higher (1.04 lower to 4.64 higher)	⊕OOO VERY LOW	CRITICAL

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Psychological status (Hospital anxiety and depression scale - depression) (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	20	-	MD 2.5 higher (0.22 lower to 5.22 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: CBT (individual face-to-face) versus GET: age and severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face)**	**GET**	**Relative (95% CI)**	**Absolute**		
Fatigue (Chalder fatigue scale) (follow-up 3-8 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15	21	-	MD 2.46 lower (7.28 lower to 2.36 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence profile: CBT (individual face-to-face) versus relaxation: adults, moderate severity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face) versus relaxation**	**Control**	**Relative (95% CI)**	**Absolute**		

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Quality of life (Quality of Life Scale) (follow-up 12 months; range of scores: 16-112; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 2.9 lower (12.95 lower to 7.15 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (self-rated global impression of change improved/much improved/very much improved) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	25/28 (89.3%)	46.4%	RR 1.92 (1.27 to 2.92)	427 more per 1000 (from 125 more to 891 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue Severity Scale) (follow-up 12 months; range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.25 lower (0.83 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 2.56 lower (17.66 lower to 12.54 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29	28	-	MD 0.45 higher (5.57 lower to 6.47 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck Anxiety Inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29	28	-	MD 0.04 higher (5.23 lower to 5.31 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (employment) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18/29 (62.1%)	34.50%	RR 1.8 (1.01 to 3.2)	276 more per 1000 (from 3 more to 759 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk) (follow-up 12 months; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 164.2 higher (78.79 lower to 407.19 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 0.07 lower (1.43 lower to 1.29 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 0.34 lower (1.94 lower to 1.26 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 16.14 higher (1.06 lower to 33.34 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Joint pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 3.62 higher (16.53 lower to 23.77 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 19: Clinical evidence profile: CBT (individual face-to-face) versus cognitive therapy: adults, moderate severity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face) versus cognitive therapy**	**Control**	**Relative (95% CI)**	**Absolute**		

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Quality of life (Quality of Life Scale) (follow-up 12 months; range of scores: 16-112; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 3.42 lower (11.41 lower to 4.57 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (self-rated global impression of change improved/much improved/very much improved) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	25/29 (86.2%)	64.3%	RR 1.34 (0.98 to 1.83)	219 more per 1000 (from 13 fewer to 534 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue Severity Scale) (follow-up 12 months; range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.5 lower (1.07 lower to 0.07 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 2.45 lower (16.59 lower to 11.69 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 2.09 higher (3.4 lower to 7.58 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck Anxiety Inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 2.49 higher (2.02 lower to 7 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (employment) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	18/29 (62.1%)	57.1%	RR 1.09 (0.71 to 1.67)	51 more per 1000 (from 166 fewer to 383 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk) (follow-up 12 months; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29	28	-	MD 29.1 higher (222.56 lower to 280.76 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.44 higher (0.74 lower to 1.62 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.74 higher (0.85 lower to 2.33 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 16.67 higher (1 to 32.34 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Joint pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 14.01 higher (5.15 lower to 33.17 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: CBT (individual face-to-face) versus anaerobic activity therapy: adults, moderate severity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face) versus anaerobic activity therapy**	**Control**	**Relative (95% CI)**	**Absolute**		

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Quality of life (Quality of Life Scale) (follow-up 12 months; range of scores: 16-112; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 6.1 higher (2.46 lower to 14.66 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (self-rated global impression of change improved/much improved/very much improved) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	25/29 (86.2%)	41.4%	RR 2.08 (1.32 to 3.29)	447 more per 1000 (from 132 more to 948 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue Severity Scale) (follow-up 12 months; range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 0.4 lower (1.08 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 18.92 higher (3.96 to 33.88 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 2.99 lower (9.41 lower to 3.43 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck Anxiety Inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29	29	-	MD 0.66 lower (5.88 lower to 4.56 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (employment) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18/29 (62.1%)	34.5%	RR 1.8 (1.01 to 3.2)	276 more per 1000 (from 3 more to 759 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk) (follow-up 12 months; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 164.2 higher (78.79 lower to 407.19 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 0.07 lower (1.43 lower to 1.29 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 0.35 higher (1.32 lower to 2.02 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 3.39 higher (14.09 lower to 20.87 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Joint pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	29	-	MD 5.79 higher (15.78 lower to 27.36 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 21: Clinical evidence profile: CBT (individual face-to-face) versus psychoeducation/pacing: children and young people, severity mixed or unclear

Quality assessment	No of patients	Effect	Quality	Importance

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT (individual face-to-face) versus psychoeducation/pacing	Control	Relative (95% CI)	Absolute		
General symptom scales (follow-up 2 years; assessed with: Self-reported global improvement - much better or very much better)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19/24 (79.2%)	90%	RR 0.88 (0.68 to 1.13)	108 fewer per 1000 (from 288 fewer to 117 more)	⊕OOO VERY LOW	CRITICAL
General symptom scales (follow-up 2 years; measured with: Strengths and Difficulties Questionnaire; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	24	20	-	MD 3.98 lower (6.51 to 1.45 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder Fatigue Scale) (follow-up 2 years; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	24	20	-	MD 1.75 lower (4.85 lower to 1.35 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning) (follow-up 2 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	24	20	-	MD 5.59 higher (11.52 lower to 22.7 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (Serious adverse events) (follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/32 (3.1%)	0%	Peto OR 7.16 (0.14 to 361.11)	30 more per 1000 (from 50 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL
Return to school or work (% school attendance over 2 weeks) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	27	-	MD 8.5 higher (12.35 lower to 29.35 higher)	⊕OOO VERY LOW	CRITICAL
Return to school or work (Work and Social Adjustment Scale) (follow-up 6 months; range of scores: 0-40; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	27	-	MD 0.8 lower (1.88 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford/1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 22: Clinical evidence profile: CBT (individual face-to-face) versus waiting list: children and young people, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT (individual face-to-face) versus waiting list**	**Control**	**Relative (95% CI)**	**Absolute**		
General symptom scales (self-rated improvement recovered or much better) (follow-up 5 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	25/35 (71.4%)	44.1%	RR 1.62 (1.05 to 2.5)	273 more per 1000 (from 22 more to 661 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Checklist Individual Strength - fatigue severity sub scale) (follow-up 5 months; range of scores: 8-56; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	35	34	-	MD 13.8 lower (20.96 to 6.94 lower)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning) (follow-up 5 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 14.1 higher (2.42 to 25.78 higher)	⊕OOO VERY LOW	CRITICAL
Return to school or work (School attendance (hours attended/total hours)) (follow-up 5 months; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 8 higher (9.41 lower to 25.41 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (Checklist individual strength – concentration sub scale) (change scores) (follow-up 5 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 13.8 lower (20.96 to 6.64 lower)	⊕OOO VERY LOW	CRITICAL
Cognitive function (Reaction time tests – simple & choice) (change scores) – simple (follow-up 5 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 12 lower (42.67 lower to 18.67 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (Reaction time tests – simple & choice) (change scores) – choice (follow-up 5 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 2 lower (26.2 lower to 22.2 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Daily pain – 0-4 scale) (change scores) (follow-up 5 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 1.85 lower (3.32 to 0.38 lower)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain & joint pain – 1-4 scale) – muscle pain (follow-up 5 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 0.3 lower (0.73 lower to 0.13 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain & joint pain – 1-4 scale) – joint pain (follow-up 5 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35	34	-	MD 0.3 lower (0.8 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): : 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 23: Clinical evidence profile: CBT (web/written) versus usual care: children and young people, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT (web/written) versus no treatment/wait list control/usual care	Control	Relative (95% CI)	Absolute		
General symptom scales (follow-up 6 months; assessed with: Self rated improvement completely recovered or much better)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	52/67 (77.6%)	26.6%	RR 2.92 (1.91 to 4.48)	511 more per 1000 (from 242 more to 926 more)	⊕⊕OO LOW	CRITICAL
Fatigue/fatigability (Fatigue severity (CIS-20)) (follow-up 6 months; range of scores: 8-56; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	67	64	-	MD 18.3 lower (22.84 to 13.76 lower)	⊕⊕OO LOW	CRITICAL
Physical functioning (Child health questionnaire physical functioning) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	67	64	-	MD 18.4 higher (12.97 to 23.83 higher)	⊕⊕OO LOW	CRITICAL
Adverse events (serious adverse events) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/67 (0%)	0%	RD 0 (-0.03 to 0.03)	0 more per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL
Return to school or work (mean school attendance @ 6 months) (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	67	64	-	MD 32.6 higher (21.66 to 43.54 higher)	⊕⊕OO LOW	CRITICAL

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[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 24: Clinical evidence profile: CBT (individual face-to-face) + biofeedback versus usual care: children and young people, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT + biofeedback (individual face-to-face) versus no treatment/wait list control/usual care	Control	Relative (95% CI)	Absolute		
Fatigue (Fatigue Assessment Scale %) (follow-up 18 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	42	-	MD 14.3 lower (18.72 to 9.88 lower)	⊕OOO VERY LOW	CRITICAL
Return to school or work (School attendance hours/month) (follow-up 18 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	42	-	MD 26.2 higher (17.62 to 34.78 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]

Other psychological interventions

Table 25: Clinical evidence profile: Education and support groups versus usual care: adults, severity mixed or unclear

Quality assessment	No of patients	Effect	Quality	Importance

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education/support group	Usual care	Relative (95% CI)	Absolute		
Quality of life (SF36 physical) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.23 lower (3.52 lower to 1.06 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (SF36 mental) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.19 higher (2.26 lower to 4.64 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Health status (HUI3)) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: -0.36-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.01 higher (0.08 lower to 0.09 higher)	⊕⊕OO LOW	CRITICAL
Fatigue (Chalder fatigue score) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision[3]	none	50	51	-	MD 0.55 higher (1.56 lower to 2.66 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (total words recalled) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision[3]	none	50	51	-	MD 0.08 lower (1.2 lower to 1.05 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (correct words) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision[3]	none	50	51	-	MD 0.04 lower (1.14 lower to 1.05 higher)	⊕⊕OO LOW	CRITICAL
Cognitive function (reaction time) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.95 higher (0.87 to 1.03 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (HADS anxiety) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.95 higher (0.87 to 1.03 higher)	⊕⊕OO LOW	CRITICAL

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Psychological status (HADS depression) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.43 lower (0.56 to 0.3 lower)	⊕⊕OO LOW	CRITICAL
Psychological status (General health Questionnaire) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-36; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.41 lower (2.8 lower to 1.98 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Normal walking speed) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.06 higher (0.37 lower to 2.49 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Shuttles walked) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 1.04 higher (0.86 to 1.22 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Perceived fatigue - modified Borg scale) (follow-up 6-12 months; measured with: Pooled 6 and 12 months data.; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	51	-	MD 0.99 higher (0.87 to 1.11 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Clinical evidence profile: Cognitive therapy versus relaxation: adults, moderate severity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cognitive therapy**	**Relaxation**	**Relative (95% CI)**	**Absolute**		
Quality of life (Quality of Life Scale) (follow-up 12 months; range of scores: 16-112; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 0.52 higher (7.81 lower to 8.85 higher)	⊕OOO VERY LOW	CRITICAL
General symptom scales (self-rated global impression of change improved/much improved/very much improved) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18/28 (64.3%)	46.4%	RR 1.38 (0.85 to 2.25)	176 more per 1000 (from 70 fewer to 580 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue Severity Scale) (follow-up 12 months; range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 0.25 higher (0.29 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical functioning) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	28	28	-	MD 0.11 lower (13.62 lower to 13.4 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 1.64 lower (6.23 lower to 2.95 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck Anxiety Inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 2.45 lower (6.96 lower to 2.06 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (employment) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	16/28 (57.1%)	42.9%	RR 1.33 (0.78 to 2.28)	142 more per 1000 (from 94 fewer to 549 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk) (follow-up 12 months; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 84.17 higher (61.81 lower to 230.15 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 1.48 lower (2.54 to 0.42 lower)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 1.08 lower (2.53 lower to 0.37 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	28	28	-	MD 0.53 lower (16.78 lower to 15.72 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Joint pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 10.39 lower (27.5 lower to 6.72 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Clinical evidence profile: Buddy/mentor programme versus Wait-list: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Buddy/mentor programme**	**Wait-list**	**Relative (95% CI)**	**Absolute**		

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Quality of Life (Quality of Life Index) (follow-up 12 months; range of scores: 0-30; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	24	-	MD 1.1 higher (1.13 lower to 3.33 higher)	⊕OOO VERY LOW	CRITICAL
General Symptom Scales (Chronic Fatigue Syndrome Symptom Rating Form) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	24	-	MD 0.9 lower (2.72 lower to 0.92 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue Severity Scale) (follow-up 4 months; range of scores: 1-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	15	15	-	MD 6.5 lower (12.13 to 0.87 lower)	⊕OOO VERY LOW	CRITICAL
Physical Functioning (SF36 Physical Functioning) (follow-up 4 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	15	15	-	MD 6.4 higher (8.08 lower to 20.88 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Perceived Stress Scale) (follow-up 4 months; range of scores: 0-16; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15	15	-	MD 0.2 lower (1.6 lower to 1.2 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (CORE-E - Overall Resource Gain) (follow-up 12 months; range of scores: 0-518; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	24	-	MD 28.53 higher (7.86 lower to 64.92 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (CORE-E - Overall Resource Loss) (follow-up 12 months; range of scores: 0-518; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	23	24	-	MD 15.91 lower (69.04 lower to 37.22 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of

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participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 28: Clinical evidence profile: Pragmatic rehabilitation versus Supportive listening: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pragmatic rehabilitation	Supportive listening	Relative (95% CI)	Absolute		
Fatigue (Chalder Fatigue Scale 11-item) (follow-up 70 weeks; range of scores: 0-11; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	81	90	-	MD 0.67 lower (1.71 lower to 0.37 higher)	⊕OOO VERY LOW	CRITICAL
Physical Functioning (SF36 Physical Functioning) (follow-up 70 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	81	90	-	MD 7.55 higher (0.47 lower to 15.57 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety (follow-up 70 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	81	90	-	MD 0.08 lower (1.52 lower to 1.36 higher)	⊕⊕OO LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression (follow-up 70 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	81	90	-	MD 0.79 lower (2.13 lower to 0.55 higher)	⊕OOO VERY LOW	CRITICAL
Sleep Quality (Jenkin's Sleep Scale) (follow-up 70 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	81	90	-	MD 0.86 lower (2.56 lower to 0.84 higher)	⊕OOO VERY LOW	CRITICAL

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[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 29: Clinical evidence profile: Pragmatic rehabilitation versus Usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pragmatic rehabilitation	Usual care	Relative (95% CI)	Absolute		
Fatigue (Chalder Fatigue Scale 11-item) (follow-up 70 weeks; range of scores: 0-11; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	81	86	-	MD 0.76 lower (1.74 lower to 0.22 higher)	⊕OOO VERY LOW	CRITICAL
Physical Functioning (SF36 Physical Functioning) (follow-up 70 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials[1]	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	81	86	-	MD 3.44 higher (4.93 lower to 11.81 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety (follow-up 70 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	81	85	-	MD 0.65 higher (0.89 lower to 2.19 higher)	⊕⊕OO LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression (follow-up 70 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	81	85	-	MD 0.18 lower (1.58 lower to 1.22 higher)	⊕⊕OO LOW	CRITICAL
Sleep Quality (Jenkin's Sleep Scale) (follow-up 70 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	81	86	-	MD 0.31 lower (1.97 lower to 1.35 higher)	⊕⊕OO LOW	CRITICAL
Exercise Performance Measure (Step-Test) - Number of Steps Completed (follow-up 70 weeks; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	42	29	-	MD 0.21 lower (1.56 lower to 1.14 higher)	⊕OOO VERY LOW	CRITICAL
Exercise Performance Measure (Step-Test) - Time Taken to Complete Steps (follow-up 70 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	41	30	-	MD 4.77 lower (10.99 lower to 1.45 higher)	⊕OOO VERY LOW	CRITICAL
Exercise Performance Measure (Borg rating of Perceived Exertion) (follow-up 70 weeks; range of scores: 6-20; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	41	30	-	MD 0.14 lower (1.12 lower to 0.84 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Clinical evidence profile: Supportive listening versus Usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Supportive listening**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Fatigue (Chalder Fatigue Scale 11-item) (follow-up 70 weeks; range of scores: 0-11; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	90	86	-	MD 0.09 lower (0.97 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL
Physical Functioning (SF36 Physical Functioning) (follow-up 70 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	90	86	-	MD 4.11 lower (12.06 lower to 3.84 higher)	⊕OOO VERY LOW	CRITICAL

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Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety (follow-up 70 weeks; range of scores: 0-21; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	90	85	-	MD 0.03 lower (1.5 lower to 1.44 higher)	⊕⊕OO LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression (follow-up 70 weeks; range of scores: 0-21; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	90	85	-	MD 0.61 higher (0.76 lower to 1.98 higher)	⊕⊕OO LOW	CRITICAL
Sleep Quality (Jenkin's Sleep Scale) (follow-up 70 weeks; range of scores: 0-20; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	90	86	-	MD 0.55 higher (1.08 lower to 2.18 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 31: Clinical evidence profile: Mindfulness and medical Qigong versus Usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mindfulness + Medical Qigong**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Quality of Life (SF36 Health Transition Score - Improvement) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	13/28 (46.4%)	59.4%	RR 0.78 (0.48 to 1.28)	131 fewer per 1000 (from 309 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 32: Clinical evidence profile: Mindfulness based cognitive therapy versus Wait-list: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness based cognitive therapy	Wait-list	Relative (95% CI)	Absolute		
Fatigue (Chalder Fatigue Scale) (follow-up 2 to 4 months; SMD used as two different scales combined; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	24	27	-	SMD 0.46 lower (1.02 lower to 0.1 higher)	⊕OOO VERY LOW	CRITICAL
Physical Functioning (SF36 Physical Functioning) (follow-up 2 to 4 months; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	25	27	-	MD 7.46 higher (5.81 lower to 20.72 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression scale sub scales) - Anxiety (follow-up 2 to 4 months; range of scores: 0-21; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	25	27	-	MD 0.84 lower (3.14 lower to 1.47 higher)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression scale sub scales) - Depression (follow-up 2 to 4 months; range of scores: 0-21; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	25	27	-	MD 1.71 lower (3.62 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL
Adverse Events (Substantive Adverse Events) (assessed with: NO CLINICALLY IMPORTANT DIFFERENCE)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious imprecision[4]	none	0/18 (0%)	0%	RD 0.00 (-0.1 to 0.1)	0 more per 1000 (from 100 fewer to 100 more)	⊕OOO VERY LOW	CRITICAL
Return to School/Work (Work and Social Adjustment Scale) (follow-up 4 months; range of scores: 0-40; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	16	19	-	MD 5.8 lower (11.72 lower to 0.12 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC/Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 33: Clinical evidence profile: Focused group therapy versus Wait-list: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Focused group therapy**	**Wait-list**	**Relative (95% CI)**	**Absolute**		
Quality of Life (Gothenburg Quality of Life Scale) (follow-up 5 months; range of scores: 18-126; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7	6	-	MD 1.7 lower (17.59 lower to 14.19 higher)	⊕OOO VERY LOW	CRITICAL
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7	6	-	MD 1.3 higher (1.1 lower to 3.7 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 34: Clinical evidence profile: The Lightning Process and specialist medical care versus specialist medical care: children and young people, moderate severity

Quality assessment	No of patients	Effect	Quality	Importance

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	The Lightning Process + Specialist medical care (SMC)	SMC	Relative (95% CI)	Absolute		
Fatigue (Chalder Fatigue Scale) (follow-up 12 months; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42	38	-	MD 4 lower (7.25 to 0.75 lower)	⊕⊕OO LOW	CRITICAL
Physical Functioning (SF36 Physical Functioning) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42	38	-	MD 18.6 higher (6.85 to 30.35 higher)	⊕⊕OO LOW	CRITICAL
Psychological Status (Spence Children's Anxiety Scale) (follow-up 12 months; range of scores: 0-114; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	27	-	MD 14.5 lower (22.35 to 6.65 lower)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	27	-	MD 2.6 lower (4.75 to 0.45 lower)	⊕OOO VERY LOW	CRITICAL
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	27	-	MD 1.8 lower (3.45 to 0.15 lower)	⊕OOO VERY LOW	CRITICAL
Pain (Visual Analogue Scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	27	-	MD 6.5 lower (19.45 lower to 6.45 higher)	⊕OOO VERY LOW	CRITICAL
Return to School/Work (School/College Attendence in the Previous Week) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34	36	-	MD 1 higher (0.2 to 1.8 higher)	⊕OOO VERY LOW	CRITICAL

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Adverse events (Serious adverse events attributable to study interventions) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	39	46	RD 0 (-0.05 to 0.05)	0 more per 1000 higher (from 50 fewer to 50 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in both study arms – serious imprecision if sample size 70-350; very serious imprecision if sample size <70

Exercise interventions

Graded exercise therapy

Table 35: Clinical evidence profile: Graded exercise therapy versus standard care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus standard care**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (EQ5D) (follow-up 52 weeks; range of scores: -0.594-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	151	-	MD 0.06 higher (0.01 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
General symptom scales (patient reported global impression of change in CFS positive/much/very much better) (follow-up 12-42 weeks)												
2 (GETSET & Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	23/113 (20.4%)	9.3%	RR 2.2 (1.16 to 4.16)	112 more per 1000 (from 15 more to 294 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: General symptom scales (patient reported global impression of change in CFS positive/much/very much better) (follow-up 12 weeks)**												

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1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	14/97 (14.4%)	6/101 (5.9%)	RR 2.43 (0.97 to 6.07)	85 more per 1000 (from 2 fewer to 301 more)	⊕OOO VERY LOW	CRITICAL
Unclear PEM subgroup: General symptom scales (patient reported global impression of change in CFS positive/much/very much better) (follow-up 42 weeks)**												
1 (Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	9/16 (56.3%)	5/17 (29.4%)	RR 1.91 (0.81 to 4.49)	268 more per 1000 (from 56 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
General symptom scales (clinical global impression of change in overall health positive vs. negative/minimal change) (follow-up 12 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/97 (17.5%)	5/101 (5.0%)	RR 3.54 (1.36 to 9.22)	126 more per 1000 (from 18 more to 407 more)	⊕⊕OO LOW	CRITICAL
General symptom scales (clinical global impression of change in overall health positive vs. negative/minimal change) (follow-up 134 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	61/127 (48%)	41.7%	OR 1.1 (0.6 to 2.02)	23 more per 1000 (from 117 fewer to 174 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 12 weeks; measured with: 0-33 and 0-42 scales; Better indicated by lower values)												
2 (GETSET & Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	119	123	-	SMD 0.66 lower (0.92 to 0.4 lower)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 12 weeks; measured with: 0-33 scale; Better indicated by lower values)**												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	97	102 (mean score in control group was 22.9)	-	MD 4.3 lower (6.3 to 2.3 lower) SMD 0.6 lower (0.88 to 0.31 lower)	⊕OOO VERY LOW	CRITICAL
Unclear PEM subgroup: Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 12 weeks; measured with: 0-42 scale; Better indicated by lower values)**												
1 (Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	22	21 (mean score in control group was 24.41)	-	MD 10.5 lower (16.65 to 4.35 lower) SMD 1.0 lower (1.64 to 0.36 lower)	⊕OOO VERY LOW	CRITICAL

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Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 134 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	127	115	-	MD 0.8 lower (2.8 lower to 1.2 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical function) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
2 (GETSET & Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	119	123	-	MD 7.68 higher (3.24 to 12.12 higher)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Physical functioning (SF36 physical function) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)**												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	97	102 (mean score in control group was 50.8)	-	MD 6.9 higher (2.2 to 11.6 higher)	⊕OOO VERY LOW	CRITICAL
Unclear PEM subgroup: Physical functioning (SF36 physical function) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)**												
1 (Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	22	21 (mean score in control group was 55.0)	-	MD 14.05 higher (0.62 to 27.48 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical function) (follow-up 134 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	127	115	-	MD 2 higher (4 lower to 8 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 12-52 weeks; range of scores: 0-21; Better indicated by lower values)												
2 (PACE & GETSET)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	241	252	-	MD 1.15 lower (1.66 to 0.64 lower)	⊕⊕OO LOW	CRITICAL
PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 12 weeks; range of scores: 0-21; Better indicated by lower values)**												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	101 (mean score in control group was 8.6)	-	MD 1.2 lower (1.9 to 0.5 lower)	⊕⊕OO LOW	CRITICAL

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<95% PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)**												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	144	151 (mean score in control group was 7.2)	-	MD 1.1 lower (1.84 to 0.36 lower)	⊕⊕OO LOW	CRITICAL
Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 12-52 weeks; range of scores: 0-21; Better indicated by lower values)												
2 (PACE & GETSET)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	241	252	-	MD 1.04 lower (1.64 to 0.45 lower)	⊕⊕OO LOW	CRITICAL
PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 12 weeks; range of scores: 0-21; Better indicated by lower values)**												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	101 (mean score in control group was 8.6)	-	MD 1.1 lower (2.0 to 0.2 lower)	⊕⊕OO LOW	CRITICAL
<95% PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)**												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	144	151 (mean score in control group was 8.0)	-	MD 1.0 lower (1.8 to 0.2 lower)	⊕⊕OO LOW	CRITICAL
Pain (numeric rating scale 0-4) - muscle pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	144	149	-	MD 0.42 lower (0.73 to 0.11 lower)	⊕OOO VERY LOW	CRITICAL
Pain (numeric rating scale 0-4) - joint pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	151	-	MD 0.26 lower (0.58 lower to 0.06 higher)	⊕OOO VERY LOW	CRITICAL
Sleep quality (Jenkins sleep scale) (follow-up 52 weeks; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	151	-	MD 1.4 lower (2.3 to 0.5 lower)	⊕⊕OO LOW	CRITICAL
Adverse events (non-serious) (follow-up 12-52 weeks)												

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2	randomised trials	serious[1]	no serious inconsistency	very serious[2,5]	no serious imprecision	none	176/257 (68.5%)	172/261 (65.9%)	RR 1.03 (0.94 to 1.12)	20 more per 1000 (from 40 fewer to 79 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Adverse events (non-serious) (follow-up 12 weeks)**												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[4]	none	27/97 (27.8%)	23/101 (22.8%)	RR 1.22 (0.76 to 1.98)	50 more per 1000 (from 55 fewer to 223 more)	⊕OOO VERY LOW	CRITICAL
<95% PEM subgroup: Adverse events (non-serious) (follow-up 52 weeks)**												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	very serious[3,5]	no serious imprecision	none	149/160 (93.1%)	149/160 (93.1%)	RR 1.0 (0.94 to 1.06)	0 more per 1000 (from 56 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious) (follow-up 12-52 weeks)												
2 (PACE & GETSET)	randomised trials	serious[1]	no serious inconsistency	very serious[2,5]	very serious[4]	none	14/257 (5.4%)	9/261 (2%)	RR 1.56 (0.69 to 3.54)	11 more per 1000 (from 6 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Adverse events (serious) (follow-up 12 weeks)**												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[4]	none	1/97 (1.0%)	2/101 (2.0%)	RR 0.52 (0.05 to 5.65)	10 fewer per 1000 (from 19 fewer to 92 more)	⊕OOO VERY LOW	CRITICAL
<95% PEM subgroup: Adverse events (serious) (follow-up 52 weeks)**												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	very serious[3,5]	very serious[4]	none	13/160 (8.1%)	7/160 (4.4%)	RR 1.86 (0.76 to 4.53)	38 more per 1000 (from 10 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (adverse reactions) (follow-up 12-52 weeks)												
2 (PACE & GETSET)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[6]	none	2/257 (0.78%)	2/261 (0%)	RD 0 (-0.02 to 0.02)	0 more per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Adverse events (adverse reactions) (follow-up 12 weeks)**												

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1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	0/97 (0%)	0/101 (0%)	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
<95% PEM subgroup: Adverse events adverse reactions) (follow-up 52 weeks)**												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	2/160 (1.3%)	2/160 (1.3%)	RR 1.0 (0.14 to 7.01)	0 fewer per 1000 (from 11 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL
Activity levels (International Physical Activity Questionnaire high vs. low/moderate level of activity prev week) (follow-up 12 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/97 (29.9%)	20.2%	OR 3.2 (1.8 to 5.69)	246 more per 1000 (from 111 more to 388 more)	⊕⊕OO LOW	CRITICAL
Return to school/work (Work and Social Adjustment Scale) (follow-up 12 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	97	102	-	MD 1.9 lower (3.7 to 0.1 lower)	⊕OOO VERY LOW	CRITICAL
Return to school/work (Work and social adjustment scale) (follow-up 134 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	126	115	-	MD 0.8 lower (3.2 lower to 1.6 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	110	118	-	MD 35.3 higher (16.84 to 53.76 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VO2 peak/aerobic capacity) (follow-up 12 weeks; Better indicated by higher values)												
3	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	42	42	-	MD 2.02 higher (0.33 lower to 4.36 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Peak power) (follow-up 12 weeks; Better indicated by higher values)												

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2	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	28	30	-	MD 7.54 higher (9.48 lower to 24.56 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Elapsed exercise test time - cycle ergometer) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	8	8	-	MD 0.6 higher (2.5 lower to 3.7 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VEpeak) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	8	8	-	MD 8 higher (5.72 lower to 21.72 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (perceived exertion – Borg scale) (follow-up 12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	serious[7]	serious[2]	Serious[4]	none	28	30	-	MD 0.64 lower (1.18 to 0.1 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments): 1. Oxford or CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]
[3] The majority of the evidence included an indirect population (downgraded by one increment): Unclear if participants had PEM (Moss-Morris 2005) or the percentage of participants with PEM was <95% (PACE trial) [PEM re-analysis]
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[5] Downgraded by 1 increment because the majority of the evidence was based on indirect outcomes (AEs not necessarily treatment-related)
[6] Downgraded by 1 increment because 1 study reported zero events in either arm and optimal information size power calculation <80%
[7] Downgraded by 1 or 2 increments because of heterogeneity, I^2=96%, p=<0.00001; random effects model used
[8] Zero events – serious imprecision if sample size 70-350; very serious imprecision if sample size <70
**See Appendix G for additional details on the rationale, methods, and results of the PEM re-analysis.

Table 36: Clinical evidence profile: Graded exercise therapy versus flexibility/relaxation treatment: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus Flexibility/relaxation treatment**	**Control**	**Relative (95% CI)**	**Absolute**		

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General symptom scales (Clinical global impression of change - much or very much better) (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	16/29 (55.2%)	8/30 (26.7%)	RR 2.07 (1.05 to 4.08)	285 more per 1000 (from 13 more to 821 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatiguability (Chalder fatigue scale total) (follow-up 12 weeks; range of scores: 0-42; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	30	-	MD 6.9 lower (11.08 to 2.72 lower)	⊕OOO VERY LOW	CRITICAL
Physical function (SF36 physical function) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	30	-	MD 14 higher (3.7 to 24.3 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Treadmill walking test duration) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	29	30	-	MD 1.4 higher (0.34 lower to 3.14 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford or CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 37: Clinical evidence profile: Graded exercise therapy versus flexibility/relaxation treatment: age and severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus Flexibility/relaxation treatment**	**Control**	**Relative (95% CI)**	**Absolute**		
General symptom scales (self-rated global impression of change - much or very much better) (follow-up 16 weeks)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19/32 (59.4%)	12/29 (41.4%)	RR 1.43 (0.85 to 2.41)	178 more per 1000 (from 62 fewer to 583 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatiguability (Chalder fatigue scale sub scales) - Mental (follow-up 16 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 0.3 lower (1.29 lower to 0.69 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatiguability (Chalder fatigue scale sub scales) - Physical (follow-up 16 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 1.5 lower (3.34 lower to 0.34 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (Stroop test) - 82 questions (follow-up 16 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 8.3 higher (0.38 to 16.22 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (Stroop test) - 95 questions (follow-up 16 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 14.4 higher (0.22 to 28.58 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 16 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 1.7 lower (3.25 to 0.15 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 16 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 2.1 lower (4.08 to 0.12 lower)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VO2peak) (follow-up 4 weeks; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	32	29	-	MD 2.7 higher (0.2 lower to 5.6 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford or CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 38: Clinical evidence profile: Graded exercise therapy versus heart rate variability biofeedback therapy: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus Heart rate variability biofeedback therapy**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF36 physical component) (follow-up 5 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15	13	-	MD 0.5 lower (8.04 lower to 7.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 mental component) (follow-up 5 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11	13	-	MD 12.7 lower (22.95 to 2.45 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatiguability (Multidimensional Fatigue Inventory) (follow-up 5 months; range of scores: 20-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11	13	-	MD 12 higher (3.27 lower to 27.27 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Patient Health Questionnaire-9) (follow-up 5 months; range of scores: 0-27; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11	13	-	MD 4.6 higher (0.67 to 8.53 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 39: Clinical evidence profile: Graded exercise therapy versus adaptive pacing therapy: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus Adaptive pacing therapy**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (EQ5D) (follow-up 52 weeks; range of scores: -0.594-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143	148	-	MD 0.05 higher (0.02 lower to 0.12 higher)	⊕⊕OO LOW	CRITICAL
General symptom scales (Clinical global impression of change positive vs. negative/minimal change) (follow-up 134 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	61/127 (48%)	38.1%	OR 1.4 (0.8 to 2.45)	82 more per 1000 (from 51 fewer to 220 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Chalder fatigue scale) (follow-up 134 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	159	159	-	MD 1.1 lower (3 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical function) (follow-up 134 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	127	118	-	MD 5.6 higher (0.3 lower to 11.5 higher)	⊕OOO VERY LOW	CRITICAL

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Psychological status (Hospital anxiety and depression scale - depression) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	149	-	MD 0.5 lower (1.23 lower to 0.23 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale - anxiety) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	149	-	MD 0.3 lower (1.17 lower to 0.57 higher)	⊕⊕OO LOW	CRITICAL
Pain (NRS 0-4) - muscle pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	151	-	MD 0.38 lower (0.7 to 0.06 lower)	⊕OOO VERY LOW	CRITICAL
Pain (NRS 0-4) - joint pain (follow-up 52 weeks; range of scores: 0-4; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	149	-	MD 0.36 lower (0.68 to 0.04 lower)	⊕OOO VERY LOW	CRITICAL
Sleep quality (Jenkins sleep scale) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	144	150	-	MD 1.3 lower (2.22 to 0.38 lower)	⊕⊕OO LOW	CRITICAL
Adverse events (non-serious) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	no serious imprecision	none	149/160 (93.1%)	95.6%	RR 0.97 (0.92 to 1.03)	29 fewer per 1000 (from 76 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious) (follow-up 52 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2,4]	very serious[3]	none	13/160 (8.1%)	9.4%	RR 0.86 (0.42 to 1.75)	13 fewer per 1000 (from 55 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (adverse reactions) (follow-up 52 weeks)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/160 (1.3%)	1.3%	RR 0.99 (0.14 to 6.97)	0 fewer per 1000 (from 11 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL
Return to school/work (Work and social adjustment scale) (follow-up 134 weeks; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	126	120	-	MD 2.1 lower (4.5 lower to 0.3 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk test) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	110	111	-	MD 41 higher (20.53 to 61.47 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford or criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM is < 95% [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 increment because the majority of the evidence was based on an indirect outcome (AEs not necessarily treatment-related)

Table 40: Clinical evidence profile: Graded exercise therapy versus intermittent exercise: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus Intermittent Exercise (IE)**	**Control**	**Relative (95% CI)**	**Absolute**		
Exercise performance measure (VO2 peak/aerobic capacity) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 1.3 lower (6.89 lower to 4.29 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Peak power) (follow-up 12 weeks; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 6.8 lower (20.11 lower to 6.51 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Elapsed exercise test time - cycle ergometer) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 1 lower (3.5 lower to 1.5 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VEpeak) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 5.7 lower (18.04 lower to 6.64 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (rated perceived exertion – modified Borg scale) (follow-up 12 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 0.20 lower (1.18.lower to 0.78 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 41: Clinical evidence profile: Graded exercise therapy versus Activity diaries: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus Activity diaries (exercise control)**	**Control**	**Relative (95% CI)**	**Absolute**		
Fatigue (Chalder fatigue scale - change scores) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34	34	-	MD 3 lower (7.67 lower to 1.67 higher)	⊕OOO VERY LOW	CRITICAL

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Psychological status (Hospital anxiety and depression scale - depression - change scores) (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	34	34	-	MD 0.1 higher (1.54 lower to 1.74 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VO2 peak - change scores) (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	34	34	-	MD 2.9 higher (0.27 to 5.53 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 42: Clinical evidence profile: Graded exercise therapy versus standard care: age and severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GET versus standard care**	**Control**	**Relative (95% CI)**	**Absolute**		
Fatigue/fatigability (Chalder fatigue questionnaire 0-11 scale) (follow-up 12 months; range of scores: 0-11; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	114	34	-	MD 6.83 lower (7.87 to 5.79 lower)	⊕⊕OO LOW	CRITICAL
Physical functioning (SF36 physical function 10-30 scale) (follow-up 12 months; range of scores: 10-30; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	114	34	-	MD 7.86 higher (6.13 to 9.59 higher)	⊕⊕OO LOW	CRITICAL
Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	114	34	-	MD 5.76 lower (7.56 to 3.97 lower)	⊕⊕OO LOW	CRITICAL

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Sleep quality (Sleep problem questionnaire) (follow-up 12 months; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	114	34	-	MD 4.02 lower (5.99 to 2.04 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 12 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	114	34	-	MD 3.01 lower (4.83 to 1.18 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Other exercise interventions

Table 43: Clinical evidence profile: Intermittent exercise versus standard care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intermittent Exercise (IE) versus standard care**	**Control**	**Relative (95% CI)**	**Absolute**		
Exercise performance measure (VO2 peak/aerobic capacity) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	8	8	-	MD 4.8 higher (2.57 lower to 12.17 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Peak power) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 14.6 higher (13.68 lower to 42.88 higher)	⊕OOO VERY LOW	CRITICAL

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Exercise performance measure (Elapsed exercise test time - cycle ergometer) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	8	8	-	MD 1.6 higher (1.86 lower to 5.06 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VEpeak) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	8	8	-	MD 13.7 higher (1.36 to 26.04 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (rated perceived exertion – modified Borg scale) (follow-up 12 weeks; range of scores: 0.-10; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	8	8	-	MD 0.5 higher (0.48 lower to 1.48 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 44: Clinical evidence profile: Orthostatic training versus Sham: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Orthostatic training versus sham**	**Control**	**Relative (95% CI)**	**Absolute**		
Fatigue/fatiguability (Fatigue Impact Scale) (follow-up 4 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	18	18	-	MD 0.4 higher (20.02 lower to 20.82 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 45: Clinical evidence profile: Qigong versus no treatment: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Qigong versus no treatment	Control	Relative (95% CI)	Absolute		
Quality of life (SF36 sub scales) - change scores - Mental health (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 12.2 higher (0.77 lower to 25.17 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - Vitality (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 1.9 lower (14.49 lower to 10.69 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - Bodily pain (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 12.9 higher (3.24 lower to 29.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - General health (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 7 lower (20.22 lower to 6.22 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - Social functioning (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 0.5 lower (22.19 lower to 21.19 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - Role emotional (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 15.3 higher (23.8 lower to 54.4 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - Physical functioning (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 3.4 lower (14.2 lower to 7.4 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - change scores - Role physical (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 1.7 higher (17.48 lower to 20.88 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue severity scale) - change scores (follow-up 6 months; range of scores: 9-63; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 0.5 lower (0.98 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VO2 max) - change scores (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[1]	none	14	14	-	MD 3.8 higher (0.95 to 6.65 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Max workload) - change scores (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 3.6 higher (12 lower to 19.2 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (Borg scale – rating of perceived exertion) - change scores (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 2.7 lower (6.2 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 46: Clinical evidence profile: Isometric yoga versus Usual care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isometric yoga	Usual care/wait-list	Relative (95% CI)	Absolute		
Fatigue (Chalder fatigue scale) (follow-up mean 9.2 weeks; range of scores: 0-42; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	15	15	-	MD 6.6 lower (11.43 to 1.77 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 47: Clinical evidence profile: Anaerobic activity therapy versus cognitive therapy: adults, moderate severity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaerobic activity therapy	Cognitive therapy	Relative (95% CI)	Absolute		
Quality of life (Quality of life scale) (follow-up 12 months; range of scores: 16-112; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 9.52 lower (15.97 to 3.07 lower)	⊕OOO VERY LOW	CRITICAL
General symptom scales (participant global impression of change - improved/much/very much improved) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12/29 (41.4%)	64.3%	RR 0.64 (0.39 to 1.08)	231 fewer per 1000 (from 392 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Fatigue severity scale) (follow-up 12 months; range of scores: 1-7; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29	28	-	MD 0.1 lower (0.74 lower to 0.54 higher)	⊕OOO VERY LOW	CRITICAL
Physical functioning (SF36 physical function) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 21.37 lower (34.73 to 8.01 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 5.08 higher (0.01 lower to 10.17 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck anxiety inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 3.15 higher (1.31 lower to 7.61 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (employment) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	10/29 (34.5%)	57.1%	RR 0.6 (0.33 to 1.09)	228 fewer per 1000 (from 383 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk test) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 135.1 lower (261.01 to 9.19 lower)	⊕OOO VERY LOW	CRITICAL
Pain (Brief pain inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.51 higher (0.72 lower to 1.74 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.39 higher (1.14 lower to 1.92 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 13.28 higher (3.27 lower to 29.83 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Joint pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 8.22 higher (10.54 lower to 26.98 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 48: Clinical evidence profile: Anaerobic activity therapy versus relaxation techniques: adults, moderate severity

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anaerobic activity therapy**	**Relaxation techniques**	**Relative (95% CI)**	**Absolute**		
Quality of life (Quality of life scale) (follow-up 12 months; range of scores: 16-112; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 9 lower (17.87 to 0.13 lower)	⊕OOO VERY LOW	CRITICAL
General symptom scales (participant global impression of change - improved/much/very much improved) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12/29 (41.4%)	46.4%	RR 0.89 (0.49 to 1.6)	51 fewer per 1000 (from 237 fewer to 278 more)	⊕OOO VERY LOW	CRITICAL

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Physical functioning (SF36 physical function) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 21.48 lower (35.85 to 7.11 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue/fatigability (Fatigue severity scale) (follow-up 12 months; range of scores: 1-7; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	29	28	-	MD 0.15 higher (0.5 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck depression inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 3.44 higher (2.23 lower to 9.11 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Beck anxiety inventory) (follow-up 12 months; range of scores: 0-63; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.7 higher (4.53 lower to 5.93 higher)	⊕OOO VERY LOW	CRITICAL
Return to school/work (employment) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	10/29 (34.5%)	42.9%	RR 0.8 (0.42 to 1.56)	86 fewer per 1000 (from 249 fewer to 240 more)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (6 minute walk test) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 50.93 lower (181.39 lower to 79.53 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief pain inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.97 lower (2.23 lower to 0.29 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Brief Pain Inventory - severity) (follow-up 12 months; range of scores: 0-10; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 0.69 lower (2.23 lower to 0.85 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Muscle pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 12.75 higher (5.25 lower to 30.75 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Joint pain numeric rating scale) (follow-up 12 months; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29	28	-	MD 2.17 lower (21.92 lower to 17.58 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): CDC 1994 criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Complementary therapies

Table 49: Clinical evidence profile: Music therapy and Traditional Chinese Medicine versus Traditional Chinese Medicine: age and severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Music therapy + TCM**	**TCM**	**Relative (95% CI)**	**Absolute**		
Psychological status (Hamilton depression scale) (follow-up 4 weeks; range of scores: 0-52; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	75	15	-	MD 1.1 lower (2.87 lower to 0.67 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hamilton anxiety scale) (follow-up 4 weeks; range of scores: 0-56; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	75	15	-	MD 1.1 lower (2.16 to 0.04 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue Scale based on Chalder Fatigue Scale) (follow-up 4 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	75	15	-	MD 2.66 lower (5.01 to 0.31 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by 1 increment) or a very indirect population (downgraded by 2 increments): 1. Study included only a subset of CFS population who also met TCM definition for liver stagnation and spleen deficiency syndrome; 2. 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 50: Clinical evidence profile: Homeopathy versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Homeopathy**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Quality of life (Functional limitations profile subscales) - Physical dimension (follow-up 7 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	43	43	-	MD 2.39 lower (6.03 lower to 1.25 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Functional limitations profile subscales) - Psychosocial dimension (follow-up 7 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	43	-	MD 3.05 lower (8.36 lower to 2.26 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue impact scale subscales) - Cognitive dimension (follow-up 7 months; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	43	43	-	MD 0.67 lower (4.18 lower to 2.84 higher)	⊕⊕OO LOW	CRITICAL

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Fatigue (Fatigue impact scale subscales) - Physical dimension (follow-up 7 months; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	43	-	MD 0.32 higher (2.91 lower to 3.55 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Fatigue impact scale subscales) - Social dimension (follow-up 7 months; range of scores: 0-40; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	43	43	-	MD 0.28 higher (6.55 lower to 7.11 higher)	⊕⊕OO LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory subscales) - General fatigue (follow-up 7 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	43	-	MD 1.35 lower (2.77 lower to 0.07 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory subscales) - Physical fatigue (follow-up 7 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	43	-	MD 0.85 lower (2.3 lower to 0.6 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory subscales) - Mental fatigue (follow-up 7 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	43	-	MD 0.65 lower (2.12 lower to 0.82 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory subscales) - Reduced activity (follow-up 7 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	43	43	-	MD 0.91 lower (2.49 lower to 0.67 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory subscales) - Reduced motivation (follow-up 7 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	43	43	-	MD 0.3 higher (1.23 lower to 1.83 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 51: Clinical evidence profile: Acupuncture versus Sham acupuncture: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture versus Sham acupuncture	Control	Relative (95% CI)	Absolute		
Quality of life (SF12 subscales) - Physical (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	50	49	-	MD 2.64 higher (0.99 lower to 6.27 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF12 subscales) - Mental (follow-up 4 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	49	-	MD 0.2 higher (3.77 lower to 4.17 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder fatigue scale subscales - 14-item) - Physical fatigue (follow-up 4 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	50	49	-	MD 1.41 lower (3.96 lower to 1.14 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder fatigue scale subscales - 14-item) - Mental fatigue (follow-up 4 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	50	49	-	MD 1.17 lower (3.08 lower to 0.74 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (GHQ12) (follow-up 4 weeks; range of scores: 0-12; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	50	49	-	MD 0.37 higher (0.74 lower to 1.48 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up 4 weeks)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	0/62 (0%)	0%	RD 0 (-0.03 to 0.03)	0 more per 1000 (from 30 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Oxford criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 52: Clinical evidence profile: Abdominal tuina versus Acupuncture: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Abdominal tuina**	**Acupuncture**	**Relative (95% CI)**	**Absolute**		
Fatigue (fatigue scale 14) (follow-up 3 months; range of scores: 0-14; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	37	35	-	MD 1.1 lower (1.96 to 0.24 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (self-rating anxiety scale) (follow-up 3 months; range of scores: 20-80; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	37	35	-	MD 3.6 lower (5.64 to 1.56 lower)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hamilton rating scale for depression) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	37	35	-	MD 0.7 lower (1.33 to 0.07 lower)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up 4 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/39 (2.6%)	2/38 (5.3%)	RR 0.49 (0.05 to 5.15)	27 fewer per 1000 (from 50 fewer to 218 more)	⊕OOO VERY LOW	CRITICAL

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Serious adverse events (follow-up 4 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	0/39 (0%)	0/38 (0%)	RD 0.00 (-0.05 to 0.05)	0 more per 1000 (from 50 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 53: Clinical evidence profile: Myelophil versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Myelophil**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Fatigue (numeric rating scale) (follow-up 12 weeks; range of scores: 0-99; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	48	49	-	MD 5.73 lower (12.79 lower to 1.33 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (visual analogue scale change score) (follow-up 12 weeks; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	48	49	-	MD 0.5 higher (0.44 lower to 1.44 higher)	⊕⊕OO LOW	CRITICAL
Fatigue (fatigue severity scale change score) (follow-up 12 weeks; range of scores: 9-63; Better indicated by lower values)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	48	49	-	MD 4.2 higher (0.99 lower to 9.39 higher)	⊕⊕OO LOW	CRITICAL
Adverse events (follow-up 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	7/48 (14.6%)	9/49 (18.4%)	RR 0.79 (0.32 to 1.96)	39 fewer per 1000 (from 125 fewer to 176 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (serious) (follow-up 12 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	0/48 (0%)	0/49 (0%)	RD 0.00 (-0.04 to 0.04)	0 more per 1000 (from 40 fewer to 40 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Dietary strategies

Table 54: Clinical evidence profile: Low sugar, low yeast diet versus Healthy eating (advice): adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low sugar, low yeast diet**	**Healthy eating (advice)**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF36 subscales) - General health (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 6.1 lower (18.57 lower to 6.37 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Physical function (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 9.9 lower (26.75 lower to 6.95 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Role function (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	19	20	-	MD 2.5 higher (19.71 lower to 24.71 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Role emotion (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	19	20	-	MD 1.6 higher (26.9 lower to 30.1 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Social function (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 8.6 lower (27.03 lower to 9.83 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Body pain (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 15.1 lower (33.94 lower to 3.74 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Vitality (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 6.4 lower (21.25 lower to 8.45 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 subscales) - Mental health (follow-up 24 weeks; range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 2.9 higher (9.71 lower to 15.51 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue: Chalder fatigue scale (14-item) (follow-up 24 weeks; range of scores: 0-42; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 1.7 lower (7.43 lower to 4.03 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale subscales) - Anxiety (follow-up 24 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 1.2 higher (1.75 lower to 4.15 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale subscales) - Depression (follow-up 24 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	19	20	-	MD 1.1 higher (1.19 lower to 3.39 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Dietary supplements

Table 55: Clinical evidence profile: Acclydine and amino acids versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acclydine + amino acids	Placebo	Relative (95% CI)	Absolute		

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Quality of life (Sickness impact profile-8) (follow-up 14 weeks; range of scores: 0-5799; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	30	27	-	MD 107.9 higher (193.97 lower to 409.77 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Checklist individual strength - fatigue severity subscale) (follow-up 14 weeks;range of scores: 8-56; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	30	27	-	MD 0.6 lower (6.91 lower to 5.71 higher)	⊕OOO VERY LO	CRITICAL
Activity levels (Actometer) (follow-up 14 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	30	27	-	MD 0 higher (12.19 lower to 12.19 higher)	⊕OOO VERY LO	CRITICAL
Adverse events ('Important' side effects) (follow-up 14 weeks)												
1	randomised trials	serious[3]	no serious inconsistency	very serious[1]	very serious[4]	none	0/30 (0%)	0%	RD 0 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence included an indirect population (downgraded by 1 increment) or a very indirect population (downgraded by 2 increments) : 1. Study included only a subset of CFS population who had a IGFBP3/IGF1 ratio >2.5; 2. 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 56: Clinical evidence profile: Polynutrient supplement versus Placebo: adults, severity mixed or unclear

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Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polynutrient supplement	Placebo	Relative (95% CI)	Absolute		
General symptom scales (Sickness impact profile-8) (follow-up 12 weeks; range of scores: 0-5799; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	26	-	MD 60 lower (381.29 lower to 261.29 higher)	⊕OOO VERY LO	CRITICAL
Fatigue (Checklist individual strength - fatigue subscale) (follow-up 12 weeks; range of scores: 8-56; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	26	-	MD 0.4 higher (3.64 lower to 4.44 higher)	⊕OOO VERY LOW	CRITICAL
Activity levels (Actometer) (follow-up 12 weeks; range of scores: 0-300; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27	26	-	MD 8.4 lower (18.62 lower to 1.82 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (nausea) (follow-up 12 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/27 (11.1%)	0%	Peto OR 7.7 (0.77 to 77.47)	110 more per 1000 (from 20 fewer to 240 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (Self-reported improvement in severity of complaints) - Completely recovered (follow-up 12 weeks)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/27 (0%)	0%	RD 0 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (Self-reported improvement in severity of complaints) - Improved (follow-up 12 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/27 (18.5%)	15.4%	RR 1.2 (0.36 to 3.99)	31 more per 1000 (from 99 fewer to 460 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (Self-reported improvement in severity of complaints) - Similar (follow-up 12 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	21/27 (77.8%)	69.2%	RR 1.12 (0.81 to 1.56)	83 more per 1000 (from 131 fewer to 388 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (Self-reported improvement in severity of complaints) - Worse (follow-up 12 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/27 (3.7%)	0%	Peto OR 7.12 (0.14 to 359.1)	40 more per 1000 (from 60 fewer to 130 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 57: Clinical evidence profile: Aribinoxylane versus Placebo: adults, severity mixed or unclear

Quality assessment								No of patients	Effect		Quality	Importance

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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aribinoxylane	Placebo	Relative (95% CI)	Absolute		
Quality of life (Patient global impression of change - improvement) (follow-up 8 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	very serious[2]	none	4/34 (11.8%)	13.3%	RR 0.88 (0.24 to 3.22)	16 fewer per 1000 (from 101 fewer to 295 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (WHOQOL-BREF subscales) - Physical wellbeing (follow-up 8 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	34	30	-	MD 1.9 lower (9.23 lower to 5.43 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (WHOQOL-BREF subscales) - Psychological wellbeing (follow-up 8 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	34	30	-	MD 2.4 higher (3.27 lower to 8.07 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (WHOQOL-BREF subscales) - Social wellbeing (follow-up 8 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	34	30	-	MD 8.2 lower (14.78 to 1.62 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life (WHOQOL-BREF subscales) - Environmental wellbeing (follow-up 8 weeks; range of scores: 0-100; Better indicated by lower values)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	34	30	-	MD 2.2 lower (7.29 lower to 2.89 higher)	⊕⊕OO LOW	CRITICAL
General symptom scales (Measure yourself medical outcomes profile 2) (follow-up 8 weeks; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	34	30	-	MD 0.4 higher (0.29 lower to 1.09 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Chalder fatigue scale 11-item) (follow-up 8 weeks; range of scores: 0-11; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	34	30	-	MD 0.3 higher (1.71 lower to 2.31 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale) - Anxiety (follow-up 8 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	serious[2]	none	34	30	-	MD 0.9 lower (3.03 lower to 1.23 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale) - Depression (follow-up 8 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	no serious imprecision	none	34	30	-	MD 0.6 higher (0.57 lower to 1.77 higher)	⊕⊕OO LOW	CRITICAL
Adverse events (serious) (follow-up 8 weeks)												
1	randomised trials	serious[3]	no serious inconsistency	very serious[1]	serious[4]	none	0/37 (0%)	0%	RD 0	0 more per 1000 (from 50 fewer to 50 more)	⊕OOO VERY	CRITICAL

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									(-0.05 to 0.05)		LOW	
Adverse events (side effects causing withdrawal) (follow-up 8 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[1]	very serious[2]	none	3/37 (8.1%)	2.9%	RR 2.76 (0.3 to 25.25)	51 more per 1000 (from 20 fewer to 703 more)	⊕OOO VERY LOW	CRITICAL

[1] The majority of the evidence included an indirect population (downgraded by 1 increment) or a very indirect population (downgraded by 2 increments): 1. Study included only a subset of CFS population with symptoms suggestive of immune activation (≥2 of: tender lymph nodes, sore throat or poor temperature control); 2. 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis]..
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4]Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 58: Clinical evidence profile: Vitamin D versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin D**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Adverse events (deaths) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	0/25 (0%)	0%	RD 0 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Fatigue (Piper fatigue scale) (follow-up 6 months; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	21	24	-	MD 0.2 higher (0.8 lower to 1.2 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale) - Anxiety (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	21	24	-	MD 0.4 higher (0.95 lower to 1.75 higher)	⊕OOO VERY LOW	CRITICAL
Psychological status (Hospital anxiety and depression scale) - Depression (follow-up 6 months; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	21	24	-	MD 1 lower (2.55 lower to 0.55 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): Study included only a subset of CFS population who also had 25OHD (serum vit D) level <75nmol/L.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4]Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

Table 59: Clinical evidence profile: Coenzyme Q10 and NADH versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Coenzyme Q10 + NADH**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Fatigue (Fatigue Index Scale) (follow-up 8 weeks; range of scores: 0-160; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	39	34	-	MD 7.9 lower (18.02 lower to 2.22 higher)	⊕OOO VERY LOW	CRITICAL
Pain (McGill pain questionnaire subscales) - Affective (follow-up 8 weeks; range of scores: 0-12; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	39	34	-	MD 2.1 higher (0.55 to 3.65 higher)	⊕OOO VERY LOW	CRITICAL
Pain (McGill pain questionnaire subscales) - Sensory (follow-up 8 weeks; range of scores: 0-33; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	39	34	-	MD 4.1 higher (0.98 to 7.22 higher)	⊕OOO VERY LOW	CRITICAL
Sleep quality (Global Pittsburgh sleep quality index) (follow-up 8 weeks; range of scores: 0-21; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	39	34	-	MD 0.9 higher (0.78 lower to 2.58 higher)	⊕OOO VERY LOW	CRITICAL
Exercise performance measure (VO2 max) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	40	-	MD 0 higher (1.54 lower to 1.54 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Perceived exertion – Borg scale – change scores) (follow-up 8 weeks; range of scores: 6-20; Better indicated by lower values)												

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1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	40	40	-	MD 0.13 higher (0.53 lower to 0.79 higher)	⊕⊕OO LOW	CRITICAL
Exercise performance measure (Max workload) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	40	40	-	MD 4.4 higher (4.61 lower to 13.41 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (moderate) (follow-up 8 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	very serious[2,4]	very serious[3]	none	0/40 (0%)	7.5%	Peto OR 0.13 (0.01 to 1.27)	65 fewer per 1000 (from 74 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] The majority of the evidence included an indirect outcome (downgraded by one increment): Adverse events not necessarily treatment-related

Table 60: Clinical evidence profile: Guanidinoacetic acid (GAA) versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Guanidinoacetic acid**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Quality of life (SF36 sub scales) - PCS (follow-up 3 months; measured with: range of scores: 0-100; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 2.4 higher (0.24 lower to 5.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (SF36 sub scales) - MCS (follow-up 3 months; measured with: range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 5.3 higher (0.84 to 9.76 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory sub scales) - General fatigue (follow-up 3 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 0.2 lower (1.24 lower to 0.84 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory sub scales) - Physical fatigue (follow-up 3 months; measured with: range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 0.1 higher (0.87 lower to 1.07 higher)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory sub scales) - Reduced activity (follow-up 3 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	14	14	-	MD 2.2 lower (3.33 to 1.07 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory sub scales) - Reduced motivation (follow-up 3 months; range of scores: 4-20; Better indicated by lower values)												

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1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 1.9 lower (3.27 to 0.57 lower)	⊕OOO VERY LOW	CRITICAL
Fatigue (Multidimensional fatigue inventory sub scales) - Mental fatigue (follow-up 3 months; range of scores: 4-20; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	14	14	-	MD 1.8 lower (2.81 to 0.79 lower)	⊕OOO VERY LOW	CRITICAL
Pain (Visual analogue scale) - At rest (follow-up 3 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	14	14	-	MD 0.2 lower (1.06 lower to 0.66 higher)	⊕OOO VERY LOW	CRITICAL
Pain (Visual analogue scale) - During activity (follow-up 3 months; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	14	14	-	MD 0.6 lower (1.83 lower to 0.63 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (Self-reported side effects) (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious imprecision	none	14/0 (0%)	0%	RD 0 (-0.13 to 0.13)	0 more per 1000 (130 fewer to 130 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4]Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

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Table 61: Clinical evidence profile: Ubiquinol-10 versus Placebo: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ubiquinol-10	Placebo	Relative (95% CI)	Absolute		
Cognitive function (Uchida-Kraepelin psychodiagnostic test) - Number of responses (follow-up 12 weeks; Better indicated by higher values)												
4	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	14	-	MD 5.7 higher (43.65 lower to 55.05 higher)	⊕OOO VERY LOW	CRITICAL
Cognitive function (Uchida-Kraepelin psychodiagnostic test) - Number of correct responses (follow-up 12 weeks;; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	17	14	-	MD 4.1 higher (46.35 lower to 54.55 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events (Serious) (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious imprecision[4]	none	0/18 (0%)	0%	RD 0 (-0.11 to 0.11)	0 more per 1000 (110 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment): 1994 CDC criteria used; PEM is not a compulsory feature [original analysis]; Percentage of participants with PEM unclear [PEM reanalysis].
[3]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4]Zero events in both arms - downgraded by 1 increment if the sample size is between 70 and 350, and downgraded by 2 increments if the sample size is <70

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Appendix G PEM reanalysis

G.1 PEM reanalysis – Methods and rationale

After considering the stakeholder comments the committee agreed to revisit the evidence for the intervention reviews further scrutinising the information on PEM reported in the trials and the application of indirectness in the evidence. In the original analysis studies were downgraded for indirectness if the diagnostic criteria used in the study did not have PEM as a compulsory feature.

We looked for any published information on the percentage of participants with PEM in the included trials, or subgroup analyses in study participants with PEM. The papers for all included studies were reviewed again, as well as any published supplements. The excluded studies list was also re-examined to ensure any relevant information relating to PEM in the included studies were not missed. Unpublished data was not accepted for this analysis.

The committee agreed that studies using criteria without PEM as a compulsory feature (e.g. 1994 CDC criteria, Oxford criteria) should not be downgraded if a high proportion of study participants had PEM and this was adequately described. In order to not downgrade the following criteria must be met:

- ≥95% of study participants are reported to have PEM (or a subgroup analysis where ≥95% participants are reported to have PEM)

AND

- If another term is used other than PEM (e.g. post-exertional fatigue) there must be a clear description that indicates all of the following:
    - Symptom worsening that follows minimal physical or mental activity that was previously tolerated
    - Symptom worsening is typically delayed (12-24 hours after the activity)
    - The impact is prolonged

OR

- ≥95% of study participants meet a diagnostic criteria where PEM is compulsory (e.g. IOM 2015, NICE 2007, Carruthers 2003/Canadian criteria).

Only new or changed results are reported below. Results for outcomes where applying the above criteria did not change the indirectness rating are not shown here. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. Additionally, results reported below have also been added throughout the report, alongside the original results. The committee's discussion of the evidence can be found in evidence review G.

G.2 PEM reanalysis – Summary of results

Self-management

No new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

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Psychological/behavioural interventions

Cognitive behavioural therapy

No new information on PEM identified that required re-analysis. See original results in Evidence review G section and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

Other psychological interventions

No new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

Exercise interventions

Graded exercise therapy

Graded exercise therapy vs usual care (adults, severity mixed or unclear)

GETSET trial participants were considered to have PEM on the basis of meeting the NICE 2007 criteria. Where outcomes from this trial and other trials with less than 95% of participants with PEM or unclear PEM percentage (PACE trial and Moss-Morris 2005) were meta-analysed, a subgroup analysis was performed to explore the results from these trials separately. These outcomes were general symptom scales (global impression of change), fatigue/fatigability (Chalder fatigue scale), physical functioning (SF36 physical functioning sub-scale), psychological status (Hospital Anxiety and Depression scale – depression and anxiety sub-scales), and adverse events (non-serious, serious, and adverse reactions).

- General symptom scales
    - There was a benefit of GET in the original analysis (meta-analysis of two studies).
    - In the subgroup analysis, the benefit remained in the PEM subgroup, but there was borderline benefit/no clinically important difference in the unclear PEM subgroup.
    - The study quality was very low in the original analysis and for both studies individually in the reanalysis.
- Fatigue/fatigability
    - There was a benefit of GET in the original analysis (meta-analysis of two studies).
    - In the subgroup analysis, the benefit remained in both the PEM and unclear PEM subgroups.
    - The evidence quality was very low in the original analysis and for both studies individually in the reanalysis.
- Physical functioning
    - There was a no clinically important difference between GET and usual care in the original analysis (meta-analysis of two studies).
    - In the subgroup analysis, there was also no clinically important difference in the PEM subgroup, but benefit of GET in the unclear PEM subgroup.

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    - The evidence quality was very low in the original analysis and for both studies individually in the reanalysis.
- Psychological status (depression, anxiety)
    - There was a no clinically important difference between GET and usual care in the original analysis (meta-analysis of two studies).
    - In the subgroup analysis, there was also no clinically important difference in the PEM and <95% PEM subgroups.
    - The evidence quality was low in the original analysis and for both studies individually in the reanalysis.
- Adverse events (non-serious, serious, adverse reactions)
    - There was a no clinically important difference between GET and usual care in the original analysis (meta-analysis of two studies).
    - In the subgroup analysis, there was also no clinically important difference in the PEM and <95% PEM subgroups.
    - The evidence quality was very low in the original analysis and for both studies individually in the reanalysis.

The committee considered the above evidence and agreed it did not change their overall interpretation of the evidence for graded exercise therapy versus standard care.

GRADE tables and forest plots are presented below.

For the remaining outcomes and comparisons there was no new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

Other exercise interventions

No new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

Complementary therapies

No new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

Dietary strategies

No new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

Dietary supplements

No new information on PEM identified that required re-analysis. See original results in Evidence review G and Appendix F (forest plots) and Appendix E (GRADE tables) in this report. The committee's discussion of the evidence can be found in evidence review G.

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G.3 PEM reanalysis – Reporting of PEM

Summary of PEM reporting in each study

Study	Intervention	Reporting of PEM	Effect on indirectness rating
Al-Haggar 2006[14]	CBT (individual face-to-face) + biofeedback vs standard care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Broadbent 2016[93] & 2017[94]	GET vs intermittent exercise vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Brouwers 2002[99]	Polynutrient supplement vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Castro-Marrero 2015[124] & 2016[126]	Coenzyme Q10 & NADH vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Chalder 2010[138] & Lloyd 2012[457]	CBT (individual face-to-face) vs psychoeducation & pacing	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Clark 2016[163] & 2017[164] (GETSET trial)	GET vs usual care	Only participants meeting the NICE 2007 criteria, which has PEM as a compulsory feature, were included.	Remain not downgraded (all participants met the NICE 2007 criteria)
Collinge 1998[183]	Mindfulness & medical qigong vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Crawley 2018[204], Crawley 2013[200] & Anon 2019[549] (SMILE Trial)	The Lightning Process + SMC vs SMC (multidisciplinary rehab consultations)	Participants diagnosed according to the NICE 2007 guidelines, which has PEM as a compulsory feature.	Remain not downgraded (all participants were diagnosed according to the NICE 2007 guidelines)
Deale 1997[225] & Deale 2001[228]	CBT (individual face-to-face) vs relaxation	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Dybwad 2007[244]	Qigong vs no treatment	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)

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Study	Intervention	Reporting of PEM	Effect on indirectness rating
Friedberg 2016[269]	Self-management programme delivered by booklet/CDs with actigraphy or step counters vs usual care	87.8% of participants had PEM (68.7% lasting >24 hours, 19.1% lasting <24 hours); 12.2% had no PEM.	Remain downgraded (<95% of participants had PEM)
Fukuda 2016[274]	Ubiquinol-10 vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Fulcher 1997[275]	GET vs flexibility/relaxation	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Guillamo 2016[299]	GET vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Hobday 2008[329]	Low sugar, low yeast diet vs health eating advice	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Huanan 2017[337]	Abdominal tuina vs acupuncture	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Janse 2018[354] (Janse 2015)[355]	Web/written CBT vs usual care	90.4% of participants had PEM. By study arm: CBT 88.8%, waitlist 93.8%.	Remain downgraded (<95% of participants had PEM)
Jason 2007[363]	CBT vs relaxation vs cognitive therapy vs anaerobic activity	PEM severity was reported as a continuous outcome, but the percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Jason 2010[361]	Buddy/mentor programme vs waitlist	PEM severity was reported as a continuous outcome, but the percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Joung 2019[375]	Myelophil vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)

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Study	Intervention	Reporting of PEM	Effect on indirectness rating
Knoop 2008[414]	Web/written CBT vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Kos 2015[419]	Activity pacing vs relaxation	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Lopez 2011[465]	Group-based CBT (cognitive behavioural stress management) vs psychoeducation	97.4% of participants had 'unusual fatigue after exertion', measured using the CDC symptom inventory which asked the question "During the past month, have you been unusually fatigued or unwell for at least one day after exerting yourself in any way?"	Remain downgraded (inadequate description of 'unusual fatigue after exertion' to confirm participants had PEM)
McDermott 2006[492]	Aribinoxylane vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Moss-Morris 2005[521]	GET vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Ng 2013[539]	Acupuncture vs sham acupuncture	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Nijhof 2011[542] & 2012[541] (FITNET trial)	CBT (web/written) vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Nunez 2011[550]	CBT (group-based) + GET vs usual care/exercise counselling	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
O'Dowd 2006[553]	Group-based CBT vs education & support groups vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Oka 2014[558]	Isometric yoga vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)

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Study	Intervention	Reporting of PEM	Effect on indirectness rating
Ostojic 2016[563]	Guanidinoacetic acid (GAA) vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Pinxsterhuis 2017[591]	Group-based self-management programme vs usual care	Participants met both the 1994 CDC criteria and the Canadian Criteria (Carruthers 2003) – the Canadian criteria has PEM as a compulsory feature.	Remain not downgraded (all participants met Canadian criteria)
Powell 2001[601]	GET vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Ridsdale 2001[631]	CBT (individual face-to-face) vs counselling	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Ridsdale 2004[630]	CBT (individual face-to-face) vs GET	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Rimes 2013[678]	Mindfulness-based cognitive therapy vs waitlist	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Sharpe 1996[678]	Individual face-to-face CBT vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Soderberg 2001[691]	Focused group therapy vs waitlist	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Stulemeijer 2005[716]	CBT (individual face-to-face) vs waiting list	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Surawy 2005[722]	Mindfulness-based cognitive therapy vs waitlist	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Sutcliffe 2010[723]	Orthostatic training vs sham	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)

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Study	Intervention	Reporting of PEM	Effect on indirectness rating
Taylor 2004[732] & 2006[733]	Buddy/mentor programme vs waitlist	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
The 2007[753]	Acclydine & amino acids vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Tummers 2012[769]	Web/written CBT vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Vos-Vromans 2016[808] (2012[809] and 2017[807]) (FatiGo trial)	CBT (individual face-to-face) vs multidisciplinary rehab	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Wallman 2004[815]	GET vs flexibility/relaxation	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Wearden 1998[836]	GET vs activity diaries	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Wearden 2006[837], 2010[834] & 2013[835] (FINE trial)	Pragmatic rehabilitation vs supportive listening vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Weatherley-Jones 2004[838]	Homeopathy vs placebo	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
White 2011[847] (White 2007[848], Walwyn 2013[816], Bourke 2014[81], Dougall 2014[239], Sharpe 2015[676]) (PACE trial)	APT vs CBT vs GET vs SMC	84.2% of participants had PEM. By study arm: APT 84%, CBT 84%, GET 82%, SMC 87%. Some outcome data was available for participants meeting the London ME criteria, but the London ME criteria does not clearly described PEM as a compulsory feature.	Remain downgraded (<95% of participants had PEM)

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Study	Intervention	Reporting of PEM	Effect on indirectness rating
Wiborg 2015[856]	Group-based CBT vs usual care	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Windthorst 2017[866]	GET vs heart rate variability biofeedback therapy	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Witham 2015[868]	Vitamin D vs placebo	Participants met both the 1994 CDC criteria and the Canadian Criteria (Carruthers 2003) – the Canadian criteria has PEM as a compulsory feature.	Remain not downgraded (all participants met Canadian criteria)
Wright 2005[874]	Self-management (activity pacing) vs Stairway to health (structured incremental rehab programme)	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)
Zhang 2015[886]	Music therapy vs traditional Chinese medicine	The percentage of participants with PEM was not reported.	Remain downgraded (percentage of participants with PEM unclear)

G.4 PEM reanalysis – GRADE tables

Graded exercise therapy

Table 62: Clinical evidence profile: Graded exercise therapy versus standard care: adults, severity mixed or unclear

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GET versus standard care	Control	Relative (95% CI)	Absolute		
PEM subgroup: General symptom scales (patient reported global impression of change in CFS positive/much/very much better) (follow-up 12 weeks)												

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1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	14/97 (14.4%)	6/101 (5.9%)	RR 2.43 (0.97 to 6.07)	85 more per 1000 (from 2 fewer to 301 more)	⊕OOO VERY LOW	CRITICAL
Unclear PEM subgroup: General symptom scales (patient reported global impression of change in CFS positive/much/very much better) (follow-up 42 weeks)												
1 (Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	9/16 (56.3%)	5/17 (29.4%)	RR 1.91 (0.81 to 4.49)	268 more per 1000 (from 56 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 12 weeks; measured with: 0-33 scale; Better indicated by lower values)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	97	102 (mean score in control group was 22.9)	-	MD 4.3 lower (6.3 to 2.3 lower) SMD 0.6 lower (0.88 to 0.31 lower)	⊕OOO VERY LOW	CRITICAL
Unclear PEM subgroup: Fatigue/fatigability (Chalder fatigue questionnaire) (follow-up 12 weeks; measured with: 0-42 scale; Better indicated by lower values)												
1 (Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	22	21 (mean score in control group was 24.41)	-	MD 10.5 lower (16.65 to 4.35 lower) SMD 1.0 lower (1.64 to 0.36 lower)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Physical functioning (SF36 physical function) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	97	102 (mean score in control group was 50.8)	-	MD 6.9 higher (2.2 to 11.6 higher)	⊕OOO VERY LOW	CRITICAL
Unclear PEM subgroup: Physical functioning (SF36 physical function) (follow-up 12 weeks; range of scores: 0-100; Better indicated by higher values)												
1 (Moss-Morris 2005)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	22	21 (mean score in control group was 55.0)	-	MD 14.05 higher (0.62 to 27.48 higher)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 12 weeks; range of scores: 0-21; Better indicated by lower values)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	101 (mean score in	-	MD 1.2 lower (1.9 to 0.5 lower)	⊕⊕OO LOW	CRITICAL

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								control group was 8.6)				
<95% PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - depression) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	144	151 (mean score in control group was 7.2)	-	MD 1.1 lower (1.84 to 0.36 lower)	⊕⊕OO LOW	CRITICAL
PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 12 weeks; range of scores: 0-21; Better indicated by lower values)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	101 (mean score in control group was 8.6)	-	MD 1.1 lower (2.0 to 0.2 lower)	⊕⊕OO LOW	CRITICAL
<95% PEM subgroup: Psychological status (Hospital Anxiety and Depression Scale - anxiety) (follow-up 52 weeks; range of scores: 0-21; Better indicated by lower values)												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	144	151 (mean score in control group was 8.0)	-	MD 1.0 lower (1.8 to 0.2 lower)	⊕⊕OO LOW	CRITICAL
PEM subgroup: Adverse events (non-serious) (follow-up 12 weeks)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[3]	none	27/97 (27.8%)	23/101 (22.8%)	RR 1.22 (0.76 to 1.98)	50 more per 1000 (from 55 fewer to 223 more)	⊕OOO VERY LOW	CRITICAL
<95% PEM subgroup: Adverse events (non-serious) (follow-up 52 weeks)												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	very serious[4,5]	no serious imprecision	none	149/160 (93.1%)	149/160 (93.1%)	RR 1.0 (0.94 to 1.06)	0 more per 1000 (from 56 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Adverse events (serious) (follow-up 12 weeks)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	serious[5]	very serious[3]	none	1/97 (1.0%)	2/101 (2.0%)	RR 0.52 (0.05 to 5.65)	10 fewer per 1000 (from 19 fewer to 92 more)	⊕OOO VERY LOW	CRITICAL
<95% PEM subgroup: Adverse events (serious) (follow-up 52 weeks)												

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1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	very serious[4,5]	very serious[3]	none	13/160 (8.1%)	7/160 (4.4%)	RR 1.86 (0.76 to 4.53)	38 more per 1000 (from 10 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
PEM subgroup: Adverse events (adverse reactions) (follow-up 12 weeks)												
1 (GETSET trial)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/97 (0%)	0/101 (0%)	RD 0 (-0.02 to 0.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
<95% PEM subgroup: Adverse events adverse reactions) (follow-up 52 weeks)												
1 (PACE trial)	randomised trials	serious[1]	no serious inconsistency	serious[4]	very serious[3]	none	2/160 (1.3%)	2/160 (1.3%)	RR 1.0 (0.14 to 7.01)	0 fewer per 1000 (from 11 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments): 1. Unclear if participants had PEM (% not reported)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments): 1. <95% of participants had PEM
[5] Downgraded by 1 or 2 increments because the majority of the evidence was based on indirect outcomes: 1. Unclear if treatment-related AEs
[6] Zero events – serious imprecision if sample size 70-350; very serious imprecision if sample size <70

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G.5 PEM reanalysis – Forest plots

Graded exercise therapy versus standard care: age and severity mixed or unclear

Figure 396: General symptom scales (patient reported global impression of change positive/much/very much better)

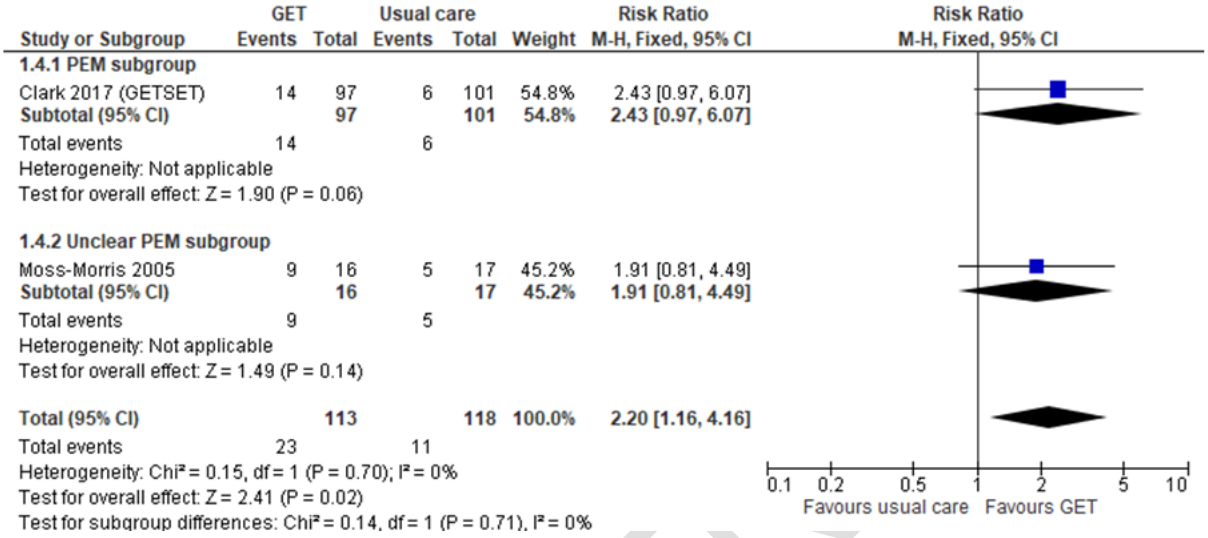


Figure 397: Fatigue/fatigability (Chalder fatigue questionnaire – SMD)

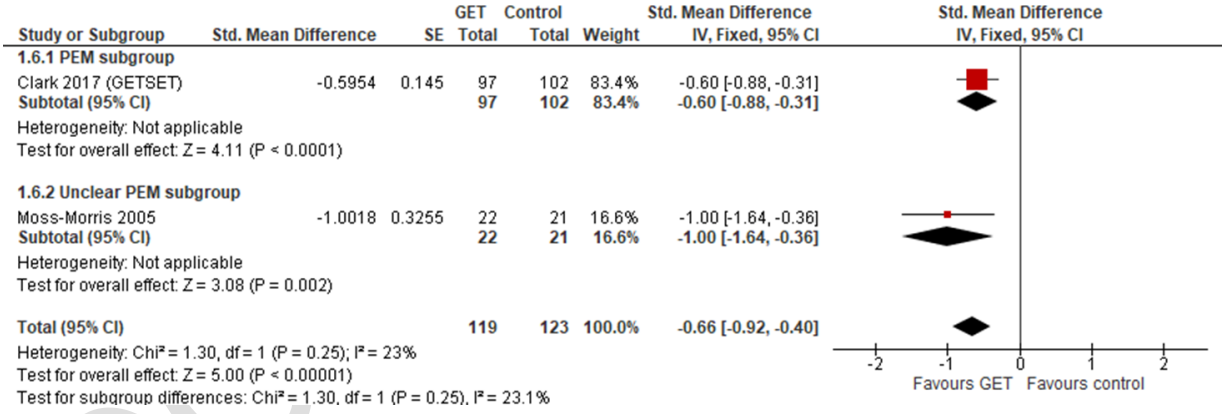


Figure 398: Fatigue/fatigability (Chalder fatigue questionnaire – 0-33 scale)

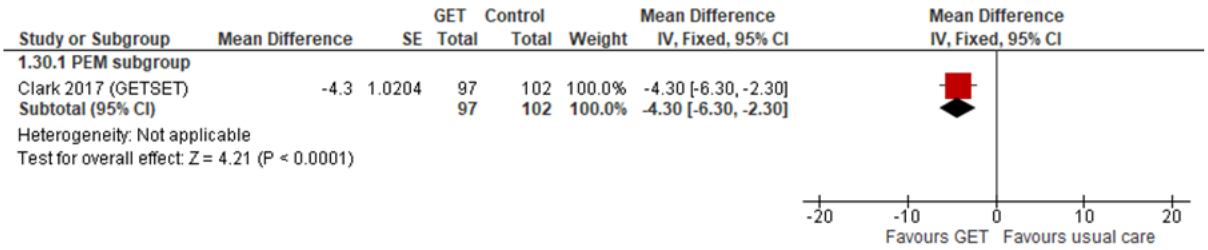
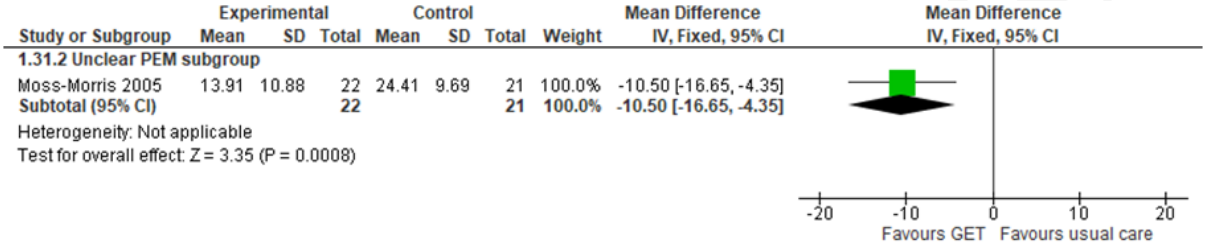


Figure 399: Fatigue/fatigability (Chalder fatigue questionnaire – 0-42 scale



Source: <Insert Source text here>

Figure 400: Physical functioning (SF36 physical function)

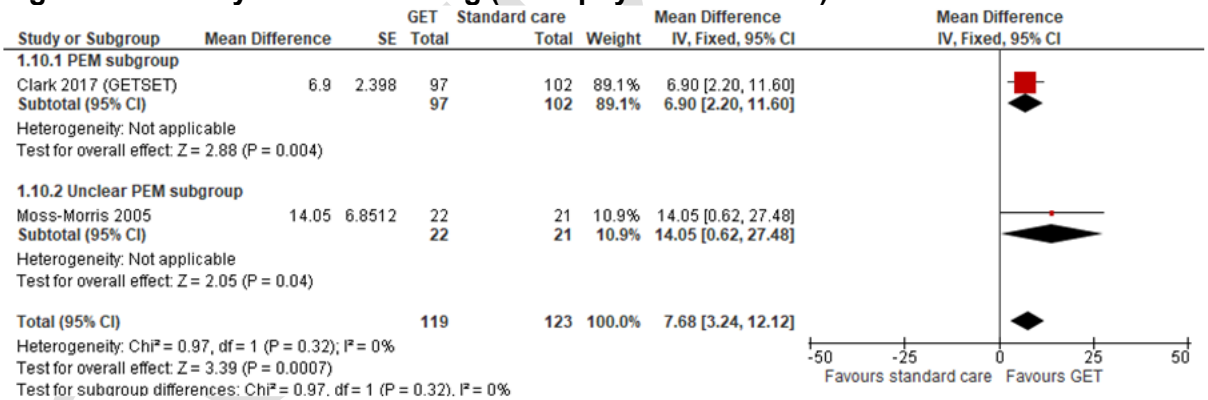


Figure 401: Psychological status (Hospital Anxiety and Depression Scale - depression)

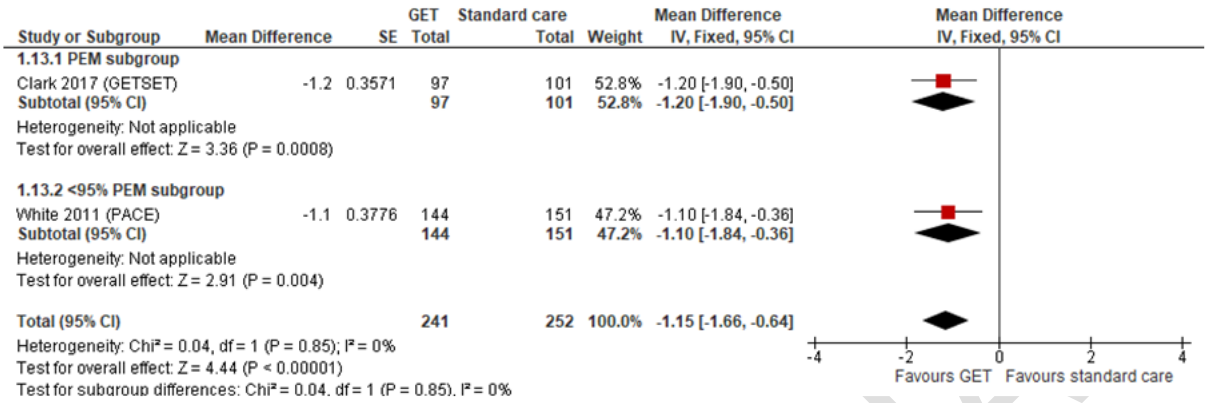


Figure 402: Psychological status (Hospital Anxiety and Depression Scale - anxiety)

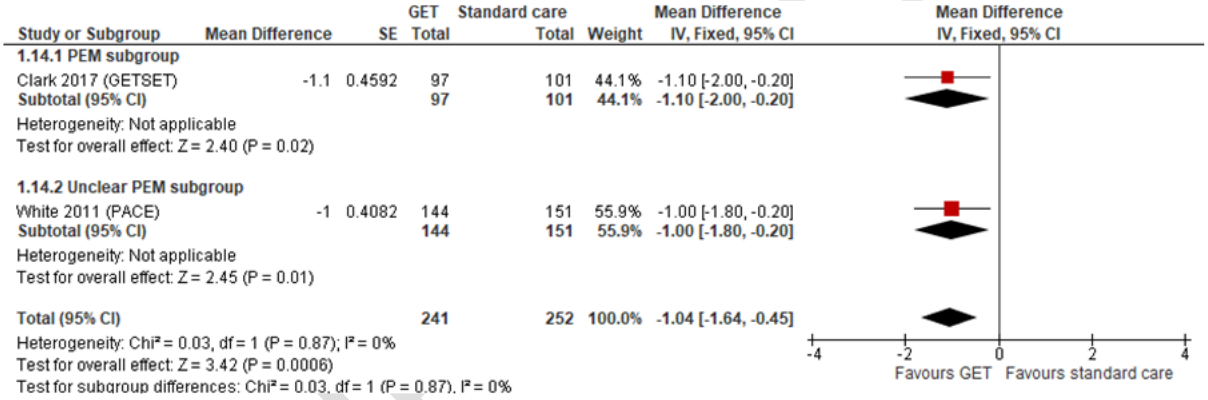


Figure 403: Adverse events (non-serious)

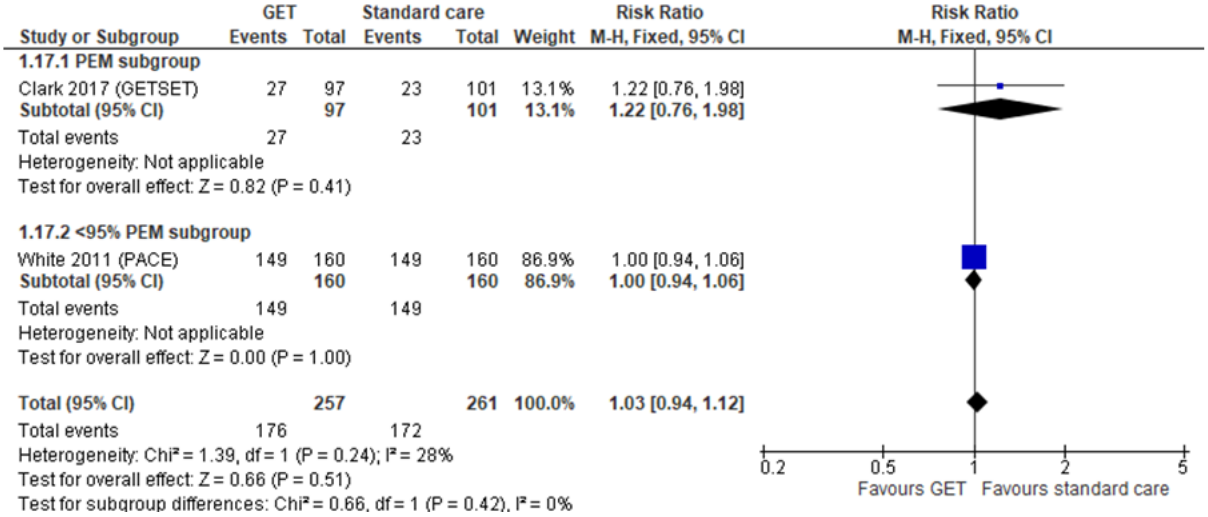


Figure 404: Adverse events (serious)

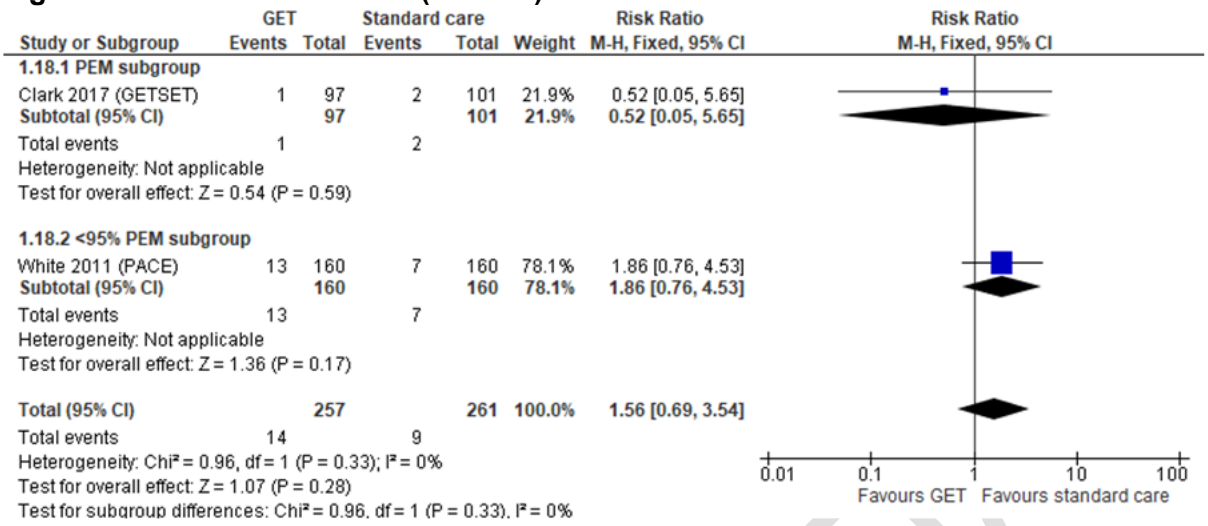
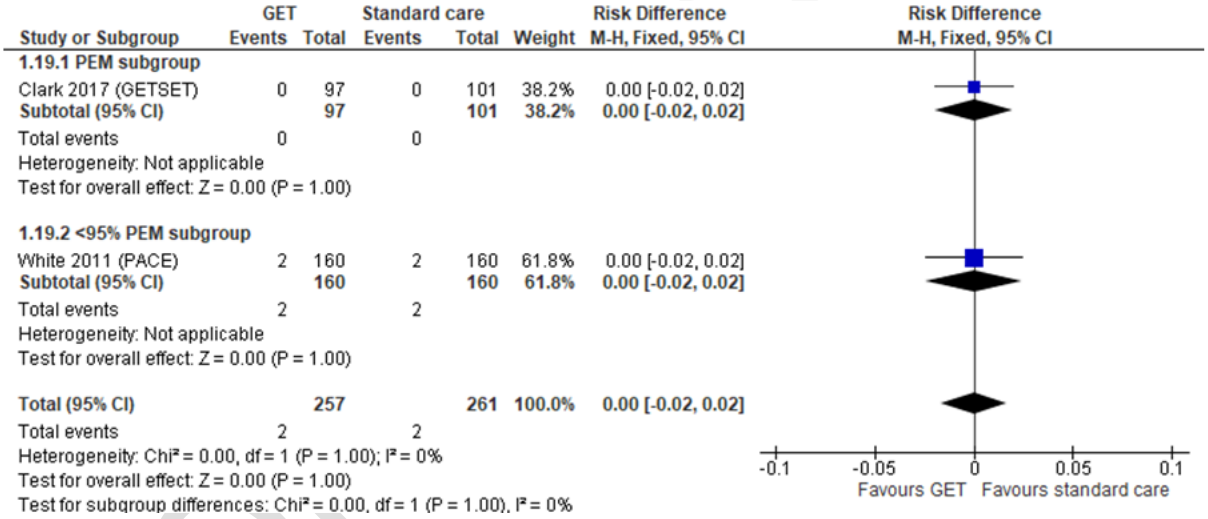


Figure 405: Adverse events (adverse reactions)



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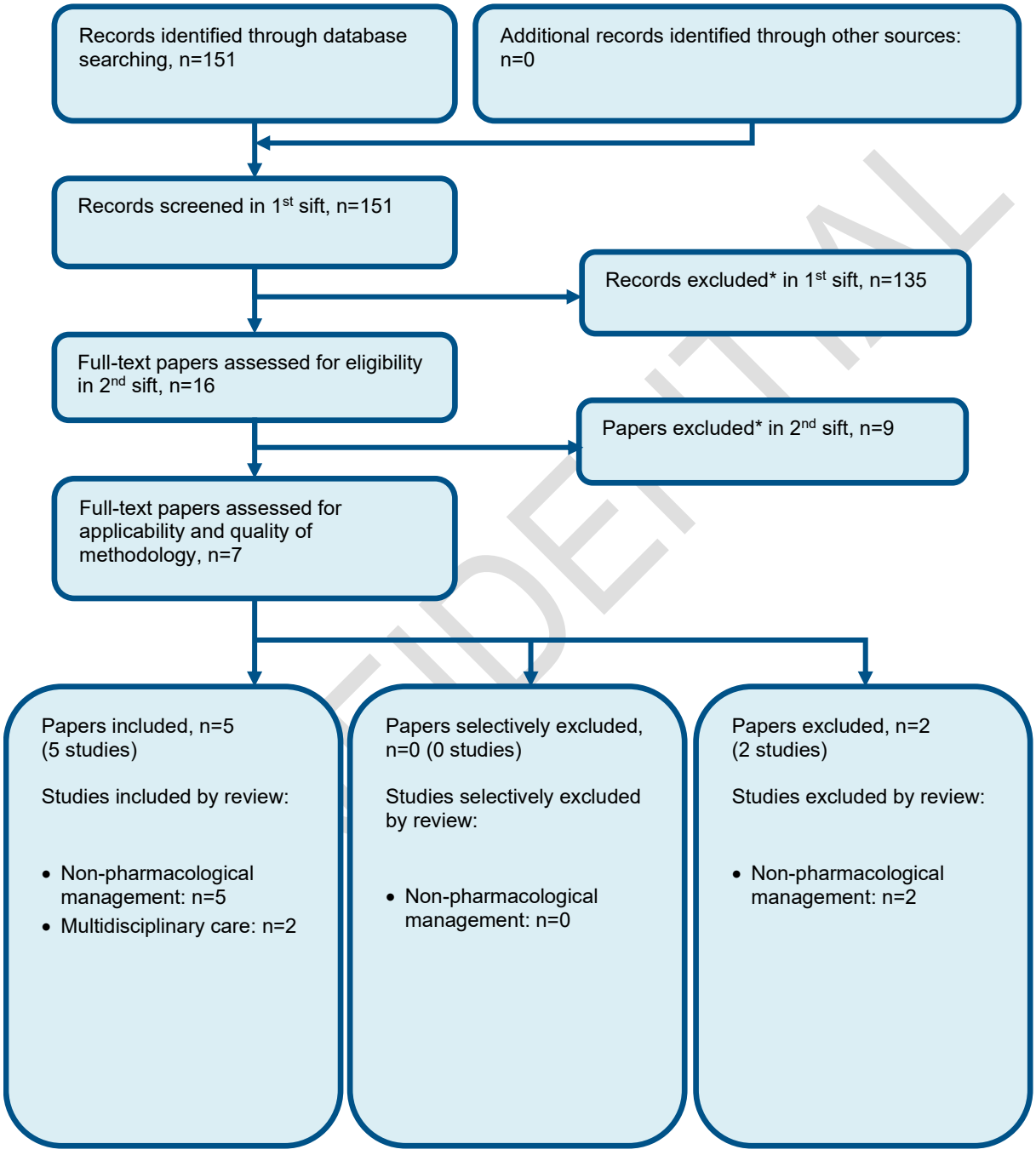
Appendix H Economic evidence study selection

Figure 406: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

NB. Two papers were included in both the non-pharma and the multidisciplinary care reviews, in parallel with the review of clinical effectiveness

Appendix I Economic evidence tables

Study	Crawley 2018[204]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Within trial analysis (RCT) **Approach to analysis:** Mean costs and mean QALYs compared over the duration of the study period (12 months) **Perspective:** NHS provider perspective **Follow-up**: 12 months **Discounting:** Costs = NR Outcomes = NR	**Population:** Children (aged 12 – 18) with diagnosed CFS/ME by the Bath/Bristol CFS/ME service according to 2007 NICE ME guidelines. **Cohort settings:** Mean age: 14.5 N: 100 Drop out: 20% **Intervention 1:** Specialist medical care (SMC) Children and families are offered a variety of treatment options that are recommended in NICE guidelines. These are typically centred around graded activity and involves a follow-up phone call at two weeks followed by family-based rehabilitation consultations lasting one hour at approximately six weeks, three months, and four and a half months. Number and timing of sessions ate agreed with the child and family according to the needs and goals of child. Furthermore, children with high levels of anxiety are offered three individual sessions of CBT every two weeks over a six-week period. **Intervention 2:** SMC and The Lightening process (LP) In addition to SMC (described in Intervention 1) young people and parents were asked to read the information about the LP on the website or using information sheets. If the child is well enough they will also be asked to read or listen to an audiobook about the LP given to them by the LP team. Children and parents will be asked to complete an assessment form (this will take 10 minutes) and describe their goals and what they have learn after	**Total costs[(a)] (mean per patient):** Intervention 1: £1604 Intervention 2: £1935 Incremental (2−1): £331 (95% CI: £130 to £531; p=NR) **Currency & cost year:** 2014 UK pounds **Cost components incorporated:** Cost of staff time in different settings (primary, community and hospital), cost of prescription medicine and intervention.	**QALYs[(b)] (mean per patient):** Intervention 1: 0.533 Intervention 2: 0.628 Incremental (2−1): 0.095 (95% CI: 0.030 to 0.160; p=NR)	**ICER [(c)] (Intervention 2 versus Intervention 1):** £3,484 per QALY gained 95% CI: NR **Analysis of uncertainty[(d)]:** Probabilistic sensitivity analysis (PSA) conducted. Non-parametric bootstrapping methods were used to calculate normally distributed 95% CIs around the incremental net benefit. Probability Intervention 2 cost effective (£20K/30K threshold): 78%/80%

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	reading/listening to the book. Following the an LP practitioner will call the parent and young person and will provide an opportunity to discuss goals, ask further questions and confirm whether they are happy to continue with the LP programme. Where the child and parent are happy to proceed the LP programme consists of three group (between 3-5 people) sessions on three consecutive days with each session 225minutes long. Participants receive a theory session and a practical session. The theory session includes taught elements on the stress response, how the mind-body interacts and how thought processes can be both helpful and negative. Language used by participants are discusses and challenged, these taught sessions are followed by a group discussion. The practical session is used to put skills learnt into practice. Participants identify a goal (e.g. standing for longer) and then are given alternative ways to prepare for this such as using different cognitive strategies before and during period in which achieving goal is completed. Participants are also asked to identify a goal (an activity which lasts up to 30 minutes long) wherein they can practise taught strategies in the afternoon and evening. The LP practitioner then arranged two follow-up phone calls with the young person and parents within two weeks of the course and then approximately six to eight weeks later.			
Data sources				
Health outcomes: Health-related quality of life (EQ-5D-Y) reported directly from patients. **Quality-of-life weights:** EQ-5D adult tariff. **Cost sources:** The resource uses were sourced from the trial and this was multiplied by unit costs from sources such as PSSRU, NHS reference costs and staff salaries from NHS agenda for change.				
Comments				
Source of funding: Funded by the Linbury Trust and the Ashden trust. Study authors were funded by the NIHR during the trial. **Limitations:** Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short. The authors have reported methods to calculate the costs of the loss of productivity incurred by patients and parents. While in the text, the authors state that they have used an NHS/healthcare perspective, they have not made it explicit that these costs have not been included.				

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Overall applicability: Directly Applicable [(e)] **Overall quality:** Minor Limitations [(f)]

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years

(a) The study assumed the cost of LP was £0 in the base-case because this was what was agreed with the providers of the LP programme in the trial. The costs presented here are from sensitivity analyses where the costs from an NHS perspective are reported including the price of LP to the NHS. These costs are calculated using a multiple imputation method to account for missing data. The complete case costs from an NHS perspective are not presented.

(b) The QALYs presented here have been calculated using a multiple imputation method. The authors explain that where one item of the EQ-5D-Y was missing the mean of the other domains was used as a proxy to replace the missing value. However, authors do not report how missing data for participants that have dropped out have been calculated. The authors do report the QALYs in the complete case; however the multiple imputation method has been included in this evidence table to be consistent with the costs which have been calculated using similar methods. Using the complete case would increase the incremental QALYs (0.080) and therefore would not change the interpretation of the results that SMC+LP is cost-effective at the £20,000 threshold.

(c) The ICER had to be calculated by the National Guideline Centre using the cost and effectiveness data presented in this table.

(d) It is unclear if, when the PSA was conducted, it assumed the cost of the LP programme was £0.

(e) Directly applicable / Partially applicable / Not applicable

(f) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**McCrone et al 2012[489]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** RCT (PACE)[847] Within-trial analysis **Approach to analysis:** The analysis was based on data collected from a parallel four-arm, multi-centre, randomised controlled	**Population:** Adults 18 years or more, recruited from consecutive new outpatients attending six secondary care specialist CFS clinics in the UK. Participants were selected using the Oxford diagnostic criteria for CFS which required disabling fatigue to be the primary problem, in the absence of an exclusionary medical or psychiatric diagnosis and a binary score of 6 or more out of 11 on the Chalder fatigue questionnaire, and a score of 65 or less out of 100 on the Short Form-36 physical function sub-scale.	**Incremental health care cost (mean per patient):** Intervention 2-1: £904 (95% CI: £613-£1205 NR; p=NR) Intervention 3-1: £823 (95% CI: £637-£1117; p=NR) Intervention 4-1: £810 (95% CI: £534-£1165 NR; p=NR) **Currency & cost year:** 2009/10 UK pounds	**Incremental QALYs (mean per patient):** Intervention 2-1: 0.0492 (95% CI: 0.01-0.09 NR; p=NR) Intervention 3-1: 0.0149 (95% CI: NR; p=NR) Intervention 4-1: 0.0343 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £18,374 per QALYs gained (pa) **ICER (Intervention 3 versus Intervention 1):** £55,235 per QALYs gained (pa) **ICER (Intervention 4 versus Intervention 1):** £23,615 per QALYs gained (pa) **Probability intervention is the most cost effective (£20K/30K threshold):** Intervention 1: 24%/8% Intervention 2: 48%/63% Intervention 3: 3%/3% Intervention 3: 25%/27%

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trial (RCT_ PACE trial)[847] **Perspective:** UK NHS (secondary care) **Time horizon/Follow-up**: 12 months **Discounting:** Costs: NA; Outcomes: NA	**Cohort settings:** Age: 37-39 N: 640 **Intervention 1:** Specialist medical care (**SMC**), at least 3 sessions **alone**. Specialist medical care was provided by chronic fatigue syndrome doctors and consisted of information about chronic fatigue syndrome, coping advice, and symptomatic pharmacotherapy. **Intervention 2:** SMC, at least 3 sessions plus cognitive behaviour therapy (**CBT**), at least 15 individual therapy sessions. This was provided by clinical psychologists or nurse therapists with the aim of changing behaviour responsible for perpetuating symptoms and disability. **Intervention 3:** SMC, at least 3 sessions plus adaptive pacing therapy (**APT**), at least 15 individual therapy sessions. Involved management of energy expenditure and activity through pacing activity supervised by an occupational therapist. **Intervention 4:** SMC, at least 3 sessions, plus graded exercise therapy (**GET**) at least 15 individual therapy sessions. This	Informal care **(mean per patient):** Intervention 1: 6507 Intervention 2: 4008 Intervention 3: 6196 Intervention 4: 4073 **Cost components incorporated:** Cost per hour of therapy, the cost per hour of consultation with patient (face-to-ace contact time), service used and medication used.		**Analysis of uncertainty:** Confidence intervals were generated around the cost differences using non-parametric bootstrapping. A CEAC was used to present the uncertainty. Sensitivity analyses were conducted around key parameters in the analyses about which assumptions had been made. Specifically they (i) estimated the cost of therapy required to reverse the findings from the initial analysis, (ii) reduced the cost of standardised medical care by 50% to reflect the possibility of it being provided by a less senior doctor. (i) The cost of CBT would need to increase by 45% and GET by 22% for the cost per QALY to reach £30,000. Therapy costs for APT would need to fall by 35% for APT to have a cost per QALY compared to SMC of £30,000. (ii) No large impact on cost-effectiveness

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	was delivered by physiotherapists with the aim of increasing exercise gradually in a personalised manner to achieve appropriate physical activity.			

Data sources
Health outcomes: The effectiveness data came from a study (PACE RCT).[847] **Quality-of-life weights:** Utility valuations were obtained from the EQ-5D questionnaire which was completed by patients in the trial at baseline, 12, 24 and 52 weeks. **Cost sources:** The cost per hour of therapy was based on the PSSRU costs of health and social care. Service use was collected during the trial using client service receipt inventory CSRI, UK national reference costs were applied. Informal care was patient-reported and valued using mean national earnings.
Comments
Source of funding: This work was supported by the UK Medical Research Council, the Department of Health for England, the Department for Work and Pensions, and the Scottish Chief Scientist Office. **Limitations:** Population were selected using the Oxford criteria and therefore might not have post exertional malaise. Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. The authors acknowledged that the time horizon of 12 months may have been insufficient to fully capture the long-term costs, and the effects and relative differences between treatments. **Other:**
Overall applicability:(b) Directly applicable **Overall quality:**(c) Minor limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; RCT: randomised controlled trial.
(a) These were reported in the cost-effectiveness acceptability curve (CEAC) form the healthcare perspective, presented for the full incremental analysis
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**O'Dowd 2006[553]**			
Study details	**Population & interventions**	**Costs (mean per patient)**	**Health outcomes (mean per patient)**	**Cost effectiveness**
Economic analysis: CEA (health outcome: HUI3) **Study design:** RCT **Approach to analysis:**	**Population:** The participants were NHS patients, currently managed in primary care. Presentation consistent with ME/CFS as described by Fukuda and colleagues,from the Centers for Disease Control and prevention N: 153 (followed up for 12 months)	**Intervention costs** Intervention 1: £0 Intervention 2: £344 Intervention 3: £344 **Health care costs:** Intervention 1: £391 Intervention 2: £285	**HUI3 - difference between 12 months and baseline:** Intervention1: 0.021 Intervention 2: 0.047	2 vs 1 CBT cost £19,000 per QALY gained vs SMC 3 vs 2

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Within-trial analysis **Perspective:** UK NHS **Time horizon/Follow-up**: 12 months **Discounting:** Costs: NA; Outcomes: NA	**Mean age:** 41.1 (SD 11.9) **Intervention 1:** **Standard Medical Care (SMC).** Patients continued to be managed in primary care **Intervention 2:** **Cognitive behavioural therapy (CBT).** 8 group sessions.The CBT used in this trial was designed to do two things: first to attempt to modify thoughts and beliefs about symptoms and illness, and second to attempt to modify behavioural responses to symptoms and illness, such as rest, sleep and activity. The ultimate goal of the treatment was to increase adaptive coping strategies and therefore reduce the distress and disability. The content of the programme included: ● Elucidation of core beliefs regarding their illness and its management. ● Monitoring of activity levels and introduction of appropriate timetable. ● Introduction to exercises designed to increase general level of fitness, balance and confidence in exercise. A range of aerobic, strength, balance and stretching exercises were taught. ● Behavioural modification of sleep patterns. ● Mood management advice. ● Goal setting. The CBT groups were introduced to a structured incremental exercise programme following a group discussion about the unhelpful nature of activity cycling, following CBT principles. The calculation of a deliberately low 'baseline' for exercise as a means of counteracting activity cycling was taught, and instructions were given about pacing up by small	Intervention 3: £376 **Drug costs** Intervention 1: £64 Intervention 2: £71 Intervention 3: £90 **Total NHS costs:** Intervention 1: £452 Intervention 2: £699 Intervention 3: £810 Incremental (2−1): +£248 Incremental (2−3): -£110 (95% CI: NR; p=NR) **Currency & cost year:** 2003 £UK **Cost components incorporated:** Intervention-therapist and administrator time Health care - GP visits, outpatient appointments, inpatient stays Drugs - SSRIs, tricyclics, hypnotics, analgesics, anti-inflammatories,	Intervention 3: 0.075 **QALYs gained** (a) 2 vs 1: 0.013 3 vs 2: 0.014	EAS cost £7,929 per QALY gained vs CBT 3 vs 1 EAS cost £13,259 per QALY gained vs SMC CBT is subject to extended dominance **Analysis of uncertainty:** Standard deviations were reported. No sensitivity or statistical analysis was conducted.

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	increments once the exercise level had been achieved successfully for several days (flexibility was allowed for patients to choose their own frequency of increments). Advice was given to patients to reduce the level of exercise considerably should a significant increase in symptoms be experienced at some stage in the future, and the balance between the risks and the benefits of prolonged rest during such a setback was explored. The management of setbacks was a specific subject included in the CBT group syllabus. **Intervention 3:** **Education and support (EAS).** 8 group sessions. The same therapists met with these groups, in the same setting, at the same time and for the same duration and frequency as the CBT groups. The focus of these groups was on the sharing of experiences and the learning of basic relaxation skills. Each week, a different relaxation exercise was taught. These groups served as a control for the non-specific effects of therapy and controlled for the effects of therapist time and attention. In order to validate the role of the physiotherapist within the EAS condition, a stretch programme was introduced. This included 16 stretches for major muscle groups in the body, and patients were advised to perform each stretch twice, in a relaxed manner. The purpose of the stretches was explained as loosening the muscles so that a state of relaxation in the muscles could be achieved. If further questions regarding exercise were asked in these groups, the group was informed that there was controversy regarding the value of aerobic exercise, and therefore we did not wish to introduce exercise if it were to be unhelpful for some patients. The physiotherapist also	benzodiazapines, other		

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	participated in the teaching of relaxation techniques, including in particular those that involved movement such as progressive muscle relaxation and slow diaphragmatic breathing.			
Data sources				
Health outcomes: HUI3 and resource use were for trial participants. **Quality-of-life weights:** HUI3. **Cost sources:** Intervention costs were clinician and administrator time. Healthcare contacts were extracted from GP records. Prescribed medication was elicited using patient questionnaires, Unit costs were from the PSSRU, NHS reference costs and prescription cost analysis.				
Comments				
Source of funding: NHS Health Technology Assessment programme **Limitations:** Population were selected using the CDC/ Fukuda criteria and therefore some might not have post exertional malaise. Treatment effects were from a single trial rather than a systematic review. Outcomes are very imprecise. There is a very high risk of bias for the effectiveness outcome due to lack of blinding and selection. HUI3 instead of EQ-5D. Costing of drugs was approximate because only broad categories were recorded with no information about quantities. The relatively short time horizon could be a limitation. There were differences at baseline including male/female ratio (CBT=46%male, EAS=24%, SMC=29%). **Other:**				
Overall applicability:[b] Partially applicable **Overall quality:**[c] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CEA= cost–effectiveness analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); NR= not reported; QALYs= quality-adjusted life years; RCT: randomised controlled trial.

(a) QALYs were calculated by the National Guideline Centre health economist by assuming a linear transition between baseline and 12 months.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

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Study	Richardson et al 2013[628]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** RCT Within-trial analysis **Approach to analysis:** The analysis was based on data collected from a single blind randomised controlled trial (FINE trial[834]). **Perspective:** UK NHS **Time horizon/Follow-up**: 70 weeks **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** Patients aged 18 or over who fulfilled the Oxford criteria for CFS/ME, scored 70% or less on the SF-36 physical functioning scale, and scored four or more on the Chalder et al fatigue scale. The Oxford criteria require that patients have a principal complaint of fatigue unexplained by other medical and psychiatric conditions. The fatigue must be of definite onset, affect both physical and mental functioning, and have been present for more than 50% of the time over the past six months. **Cohort settings:** N: 296 **Intervention 1:** Treatment as Usual (**TAU**), the GPs were asked to manage their cases as they saw fit, but not to refer for systematic psychological therapies for CFS/ME during the 18 week treatment period. **Intervention 2:** Pragmatic Rehabilitation (**PR**); A programme of graded return to activity is designed collaboratively by the patient and the therapist on the basis of a physiological dysregulation model of CFS/ME. The rehabilitation programme encourages patients to regularise their sleep patterns and includes relaxation	**Incremental cost (mean per patient[(a)]):** Intervention 2-1: £218 (95% CI: -£474 to £911 NR; p=NR) Intervention 3-1: £460 (95% CI: -£250 to £1169; p=NR) **Currency & cost year:** 2008/09 UK pounds **Cost components incorporated:** Costs include: hospital services (inpatient, outpatient, A&E, day case surgery), day services (day centre, drop-in centre or social club), and contacts with health professionals over the time period of	**Incremental QALYs (mean per patient[(a)]):** Intervention 2-1: -0.012 (95% CI: -0.088 to 0.065; p=NR) Intervention 3-1: -0.042 (95% CI: -0.122 to 0.038; p=NR)	**Intervention 2 versus Intervention 1:** TAU dominant (lower cost and better outcomes) Probability Intervention 1 is cost effective (£20K/30k threshold): 64.5% / 62.6% **(Intervention 3 versus Intervention 1:** TAU dominant (lower cost and better outcomes) **Analysis of uncertainty:** Complete case analysis (excluding patient with missing data) was carried out as a sensitivity analysis. The complete case analysis suggested that PR has higher QALYs than TAU with wide confidence intervals, £39583 per QALY (calculated as £475/0.012). SL is dominated by TAU.

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	exercises to address the somatic symptoms of anxiety. We added a further component to address the concentration and memory problems that many patients experience, over ten sessions. **Intervention 3:** Supportive listening (**SL**); A listening therapy based on non-directive counselling in which the therapist aims to provide an empathic and validating environment in which the patient can discuss his or her concerns and work towards resolution of whichever problems the patient wishes to prioritise, this was carried out over ten sessions.	the trial, prescribed medications and the cost of delivering the intervention, in terms of nurse time, travel and training was also included.		
Data sources				
Health outcomes: The effectiveness data came from an RCT (FINE trial).[834] Utility valuations were obtained from the EQ-5D questionnaire which was completed by patients in the trial at baseline, 20, and 70 weeks.. **Quality-of-life weights:** EQ-5D UK tariff. **Cost sources:** The cost of NHS staff/ therapists, were based on the PSSRU costs of health and social care. Hospital visits and procedures were based on the NHS reference costs. Medication costs were obtained from the BNF.				
Comments				
Source of funding: UK Medical Research Council (G200212) and Department of Health. **Limitations:** Population were selected using the Oxford criteria and therefore some might not have post exertional malaise. Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. The authors acknowledged that the time horizon of 12 months may have been insufficient to fully capture the long-term costs, and the effects and relative differences between treatments. Outcomes are very imprecise. **Other:**				
Overall applicability:(b) Directly applicable	**Overall quality:**(c) Potentially serious limitations			

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; RCT: randomised controlled trial.

(a) Results after adjusting for differences in baseline EQ-5D, N = 296, with imputation of missing data in 23 patients who were followed up at only one time point and 19 patients who only had baseline data

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

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Study	Vos-Vromans, 2017[807]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** Within trial analysis (RCT) **Approach to analysis:** Mean costs and mean QALYs compared over the duration of the study period (12 months). **Perspective:** Dutch provider perspective [(a)] **Follow-up:** 12 months **Treatment effect duration:** 12 months **Discounting:** Costs = NR Outcomes = NR	**Population:** Patients aged between 18-60 who meet the US centres for disease control and prevention (CDC-94) criteria and have a CIS fatigue subscale score of ≥40 **Cohort settings:** Mean age: Intervention 1 = 40.4, Intervention 2 = 41.6 N = 109 **Intervention 1:** Individual cognitive behavioural therapy (CBT) is a psychotherapeutic approach where a model of perpetuating cognitions and behaviours of CFS is used to explain the persistence of CFS. These perpetuating factors include: 'high physical attributions' which will decrease physical activity and increase fatigue and functional impairment; low sense of control over symptoms and focussing on physical sensations have a direct causal effect on fatigue severity and functional impairment; a perceived lack of social support also increases the fatigue severity and functional impairment. The CBT programme occurs over 16 therapy sessions, spread over 6 months, the first 6 weeks the patient has weekly sessions followed by a single session every 2 weeks for the remaining 20 weeks. The CBT intervention has three key phases: intake, gradual reactivation and finally prevention of relapse phase. 1) Intake – Four sessions occur in four weeks, patient is asked about: cause and course of the complaints, the present complaints, illness beliefs and illness behaviour, coping, social interactions/participation, and the expectations and personal goals of the patient. Therapist tries to determine patient's activity level and categorises patient as relatively active or low activity patient. Therapist explains the model of perpetuating cognitions and behaviours of CFS and how to overcome CFS by changing patterns of thinking and changing behaviour.	**Health care costs (mean per patient):** Intervention 1: £2816 Intervention 2: £7650 Incremental (2−1): £4835 (95% CI: £3942 to £5781; p=NR) **Patient & family costs (mean per patient):** Intervention 1: £1392 Intervention 2: £2571 Incremental (2−1): -£1240 (95% CI: -£2953 to £124; p=NR) **Currency & cost year:** 2012 euros (presented here as 2012 UK pounds[(b)]) **Cost components incorporated:** General practitioner care, mental healthcare specialist, paramedical care,	**QALYs (mean per patient):** Intervention 1: 0.60 Intervention 2: 0.65 Incremental (2−1): 0.05 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £105,975 **Analysis of uncertainty:** A probabilistic sensitivity analysis (PSA) was conducted which reported that the estimated probability MRT was cost-effective when compared to CBT at the £20K/30K threshold: 0%/0%[(c)]

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	2) Gradual reactivation - Graded exercise therapy is used to gradually increase physical activity at home (walking and bicycling). The schedule is provided by the therapist according to patient's personal goals. Patient receives feedback at the following therapy session about the changes to their activity and importance is also placed on the balance between different activities with emphasis placed on patient's personal responsibility to see to the schedule. Increases to social/mental activities can also be scheduled if needed. During dialogue between patient and increasing exercise at home, patient is taught to change negative believes regarding symptoms of fatigue self-expectations and self-esteem. Lifestyle advice is provided if deemed appropriate. Sleep/wake rhythm is encouraged immediately at start of the treatment and sleeping during the day is not allowed. A plan to return to work is also organised. 3) Prevention of relapse – Patients are encouraged to cope with disturbances which may arise from sleep/wake rhythm normalisation and activity increase by using techniques learned during therapy. In the relatively active patient group, they are taught to spread out activities during the day and to be active within physical and mental boundaries. For patients with low activity level, activities will be increased from beginning of therapy. **Intervention 2:** Individual multidisciplinary rehabilitation treatment (MRT) uses a biopsychosocial model of CFS including biological, physical and psychosocial aspects. In the biopsychosocial model of CFS various precipitating, predisposing and perpetuating factors are merged, suggesting that multiple pathways may lead to the causation and persistence of CFS. The protocol of the MRT varies between patients based on treatable components (precipitating, predisposing and perpetuating factors), present complaints and personal needs of a patient. The MRT intervention has three phases including observation, treatment and prevention of relapse.	medical specialist care, hospital care, medication and over the counter medication, alternative healers, company physician and cost of intervention.		

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	1) Observation – 2 week period where therapists (psychologist, social worker, physical therapist and occupational therapist) get acquainted with patient. Patients are asked the cause and course of the complaints, the present complaints, illness beliefs and illness behaviour, coping, the social environment the patient lives in, expectations and personal goals. Psychologist (two 1hr sessions) elaborates on psychological history, present psychological wellbeing, use of medical care including medication, stress factors, cognitions, attitudes and mood (state of mind). The social worker (two 1hr sessions) assesses the social context in which the patient lives (relationships, family and role in a family), work situation and communication. The physical therapist (five 30minute sessions) makes an estimation of the physical condition and the patient's body awareness. The occupational therapist (four 30minute sessions) aims at ergonomics, lifestyle, day/week schedule and the variety of activities during the day/week. The therapists and rehabilitation physician discuss the components and methods that will be used ruing the treatment phase. The results of this meeting will be discussed with patient who will sign a contract committing to the proposed therapy. 2) Treatment – Two weeks after observation phase, the treatment phase starts which lasts 10 weeks. The type of method use depends on patient goals/need this includes: body awareness therapy (increased awareness and consciousness of the body and relation to psychological wellbeing); cognitive behaviour therapy; gradual reactivation initially under close supervision of physical therapist and occupational therapist; pacing where patient is taught to pace their activities during the day/week this will occur in the second phase of treatment where patient is given greater autonomy and responsibility to manage activities based on their experience; principles of mindfulness; normalising of sleep/wake rhythm with sleeping during the day being stopped immediately; social reintegration under supervision of the occupational therapist and social worker.			

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	3) Prevention of relapse - Six weeks after end of treatment patient visits the social worker and then 13 weeks after end of treatment patient will visit two therapists of their choice.			
Data sources				
Health outcomes: Health-related quality of life (EQ-5D-3L) reported directly from patients. **Quality-of-life weights:** The EQ-5D UK was used in the base case and Dutch tariff in a sensitivity analysis. **Cost sources:** Resource use from within RCT; costs reported as the mean costs incurred per patient for the trial duration (2008 – 2011). Medication costs were based on the tariffs from Dutch College of Health Insurance, costs for CBT or MRT treatment hours calculated using the Dutch diagnosis-dependent treatment combination also known as DBC.				
Comments				
Source of funding: Netherlands Organisations for Health Research and Development, Rehabilitation Fund, Foundation Nutsohra **Limitations**: Population were selected using the CDC/ Fukuda criteria and therefore some might not have post exertional malaise. Treatment effects were from a single trial rather than a systematic review. There is a high risk of bias for the effectiveness outcome due to lack of blinding. Time horizon might be too short. Another limitation of this study is that it has used the DBC to calculate the cost of each intervention. The DBC payment is where hospitals are reimbursed a fixed fee for a combination of diagnosis and treatment for example in this study a participant who required 49-129 hours of rehabilitation treatment would incur a cost of £3027 however, given that the duration is so broad, resource uptake of an individual requiring 49 hours versus 129 hours would be substantially different. Therefore, there is uncertainty around the true costs of CBT and MRT. Unclear how QALYs calculated. Difference in QALYs at baseline but controlled for using regression analysis.				
Overall applicability: Partially Applicable [(d)] **Overall quality:** Minor limitations [(e)]				

Abbreviations: CUA= cost–utility analysis; da= deterministic analysis; DBC= Diagnosis Treatment Combination (DBC) case-mix System; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) All costs and ICERs were recalculated by the National Guideline Centre to report a provider perspective, in keeping with the NICE reference case.

(b) Converted using [2014] purchasing power parities[562]

(c) It is unclear which QALY estimate has been used to determine the probability that MRT was cost-effective when compared to CBT at different thresholds.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

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Appendix J Excluded studies

J.1 Excluded clinical studies

Table 63: Studies excluded from the clinical review

Study	Exclusion reason
Adams 2009[6]	Systematic review is not relevant to review question or unclear PICO (Cochrane review with different population, no included studies and later withdrawn)
Adams 2018[7]	Systematic review is not relevant to review question or unclear PICO – withdrawn Cochrane review
Adamson 2020[9]	Incorrect study design (non-randomised study)
Alegre 2010[16]	Article not in English
Alraek 2011[20]	Systematic review is not relevant to review question or unclear PICO
Anderson 2019[21]	Study protocol amendment
Anon 2002[26]	Article
Anon 2016[428]	Systematic review is not relevant to review question or unclear PICO – duplicate
Anon 2019[4]	Summary article
Anon 2019[27]	Duplicate
Arring 2018[35]	Systematic review is not relevant to review question or unclear PICO
Ascough 2020[40]	Systematic review is not relevant to review question or unclear PICO
Bakker 2011[48]	Not review population
Bao 2008[50]	Article not in English
Baos 2018[51]	Study protocol
Barrett 1992[55]	Unpublished master's thesis
Bazelmans 2005[62]	Incorrect study design – non-randomised
Behan 1990[67]	No relevant outcomes – no validated measurement scales reported
Bleijenberg 2008[75]	Trial registry record
Bleijenberg 2008[74]	Trial registry record
Bleijenberg 2009[73]	Trial registry record
Brigden 2016[86]	Study protocol
Brigden 2019[85]	No relevant outcomes
Brown 2019[102]	Editor's note
Bruun Wyller 2006[104]	Summary of a systematic review; full article not in English
Burgess 2004[112]	Inappropriate comparison – compares different versions of the same treatment, CBT
Burgess 2012[111]	Inappropriate comparison – compares different types of the same treatment
Campagnolo 2017[116]	Systematic review is not relevant to review question or unclear PICO
Campion 1998[117]	Citation only
Castro-Marrero 2017[125]	Incorrect study design – non-systematic review

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Study	Exclusion reason
Chalder 1997[141]	Not review population – no diagnosis of ME/CFS
Chalder 2003[139]	Not review population – no diagnosis of ME/CFS
Chalder 2004[137]	Citation only
Chalder 2015[140]	Secondary analysis of trial data; outside protocol
Chambers 2006[142]	Systematic review is not relevant to review question or unclear PICO
Chan 2013[144]	Not review population – no diagnosis of ME/CFS
Chan 2014[143]	Not review population – no diagnosis of ME/CFS
Chan 2017[145]	Not review population – no diagnosis of ME/CFS
Chan 2019[147]	Summary of excluded trials
Chen 2008[150]	Article not in English
Chen 2010[152]	Article not in English
Chen 2018[151]	Incorrect comparison; trial compared 2 different types of acupuncture
Chisholm 2001[159]	HE evaluation of RCT data presented more fully in Ridsdale 2000 (included paper)
Cho 2005[160]	Systematic review is not relevant to review question or unclear PICO
Cho 2009[161]	Not review population – no diagnosis of ME/CFS
Cleare 2015[168]	Systematic review is not relevant to review question or unclear PICO
Collard 2019[174]	Systematic review is not relevant to review question or unclear PICO
Corbitt 2018[187]	Systematic review is not relevant to review question or unclear PICO
Courtois 2014[191]	Abstract only
Courtois 2015[192]	Systematic review is not relevant to review question or unclear PICO
Cox 1991[193]	No relevant outcomes
Crawford 2012[194]	Letter to editor
Crawley 2012[197]	Citation only
Crawley 2013[200]	No relevant outcomes; full study published elsewhere
Dannaway 2018[208]	Systematic review is not relevant to review question or unclear PICO; references to included studies not provided
De Becker 2001[218]	Citation only
Deale 1996[226]	Citation only
Deale 1998[227]	No relevant outcomes
Deale 1999[224]	Citation only
Edmonds 2004[246]	Previous version of a review
Ferrar 2017[258]	Protocol for pilot RCT
Field 1997[259]	No usable outcome data – variability statistics not reported
Forsyth 1999[266]	No relevant outcomes
Friedberg 1994[272]	Incorrect study design – non-randomised
Friedberg 2013[273]	Not review population – 61% had no diagnosis of ME/CFS and results for those with CFS not reported separately
Galeoto 2018[276]	Systematic review is not relevant to review question or unclear PICO

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Study	Exclusion reason
Geraghty 2018[282]	Systematic review is not relevant to review question or unclear PICO
Gibson 1999[286]	Incorrect study design – non-randomised
Godfrey 2000[292]	Citation only
Goldsmith 2015[294]	No relevant outcomes reported
Gordon 2010[295]	Inappropriate comparison – compares different versions of the same treatment, GET (aerobic vs resistance)
Groeger 2013[298]	No relevant outcomes
Guo 2007[303]	No relevant outcomes
Guo 2015[302]	Article not in English
Hall 2017[307]	Inappropriate comparison – compares different forms of delivery of the same intervention, CBT
Hartz 2004[315]	Not review population – no diagnosis of ME/CFS
Hlavaty 2011[327]	No relevant outcomes
Ho 2012[328]	Not review population – no diagnosis of ME/CFS
Houghton 2011[336]	Not review population – self-perceived fatigue
Huibers 2005[340]	Article not in English
Janse 2016[353]	Not review population – idiopathic chronic fatigue
Jason 2007[364]	No relevant outcomes
Jason 2009[356]	No relevant outcomes
Jia 2016[370]	Article not in English
Jiang 2015[371]	Article not in English
Jones 2017[373]	Systematic review is not relevant to review question or unclear PICO
Kaslow 1989[379]	No useable outcome data
Kim 2013[387]	Not review population – idiopathic chronic fatigue
Kim 2013[386]	Not review population – idiopathic chronic fatigue
Kim 2013[388]	Not review population – CFS and idiopathic chronic fatigue
Kim 2013[391]	Systematic review is not relevant to review question or unclear PICO
Kim 2015[389]	Not review population – CFS and idiopathic chronic fatigue
Kim 2020[385]	Systematic review is not relevant to review question or unclear PICO
King 1999[405]	citation only
Knight 2013[408]	Systematic review is not relevant to review question or unclear PICO
Knoop 2004[415]	Citation only
Kos 2012[418]	citation only
Larun 2014[432]	Systematic review is not relevant to review question or unclear PICO
Larun 2016[433]	Systematic review is not relevant to review question or unclear PICO
Larun 2017[427]	Systematic review is not relevant to review question or unclear PICO (Cochrane review using different methodologies and outcomes)
Larun 2019[429]	Systematic review is not relevant to review question or unclear PICO

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Study	Exclusion reason
Lee 2015[436]	Not review population – idiopathic chronic fatigue
Leone 2006[439]	Not review population – no diagnosis of ME/CFS
Li 2016[443]	Article not in English
Li 2017[444]	Not review population – no diagnosis of ME/CFS (self-reported)
Li 2017[445]	Article not in English
Liu 2010[454]	Article not in English
Liu 2010[453]	Article not in English
Lloyd 1993[456]	Pharma vs non-pharma; considered in pharma review
Loades 2016[462]	Systematic review is not relevant to review question or unclear PICO
Loy 2016[467]	Systematic review is not relevant to review question or unclear PICO
Lu 2014[468]	Article not in English
Malaguarnera 2008[475]	Not review population – no diagnosis of ME/CFS; frail elderly population
Malouff 2008[476]	Incorrect study design – meta-analysis
Marques 2012[479]	Protocol
Marques 2015[478]	Not review population – idiopathic chronic fatigue
Marques 2015[480]	Systematic review is not relevant to review question or unclear PICO
Marques 2017[481]	Not review population – idiopathic chronic fatigue
Martin 1994[484]	No useable outcome data
Mccrone 2004[488]	Not review population – no diagnosis of ME/CFS
Mckendrick 1999[496]	Citation only
Meeus 2010[502]	No relevant outcomes
Meeus 2015[503]	Systematic review is not relevant to review question or unclear PICO
Meng 2014[506]	Not review population – no diagnosis of ME/CFS
Meng 2017[505]	Cost effectiveness analysis of an included RCT
Mikolasek 2018[509]	Systematic review is not relevant to review question or unclear PICO
Morriss 1996[520]	Citation only
Nijhof 2013[543]	Inappropriate comparison; long term follow up after the control group had crossed over into the intervention arm (Nijhof 2012)
Nijs 2007[545]	Incorrect interventions
O'Dowd 2000[551]	Citation only
O'Dowd 2005[552]	Citation only
Park 2016[568]	Incorrect intervention – treatment (human placental extract/Laennec®) not licensed for use in the UK
Plioplys 1997[595]	Incorrect study design – non-randomised
Polo Ferrández 2020[597]	Article not in English
Porter 2010[599]	Systematic review is not relevant to review question or unclear PICO
Powell 2004[600]	Inappropriate comparison; long term follow up of Powell2001 and control group had received the intervention
Price 2000[604]	Systematic review is not relevant to review question or unclear PICO

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Study	Exclusion reason
Price 2008[603]	Systematic review is not relevant to review question or unclear PICO (Cochrane review with different population and outcomes)
Prins 2001[606]	Not review population; also includes ICF
Puetz 2008[609]	Not review population – no diagnosis of ME/CFS
Raijmakers 2019[612]	Incorrect population (Q fever fatigue syndrome)
Rao 2009[615]	No useable outcome data
Richardson 2013[628]	Cost effectiveness analysis of an included RCT (FINE)
Ridsdale 2012[632]	Not review population – no diagnosis of ME/CFS
Rimes 2005[633]	Systematic review is not relevant to review question or unclear PICO
Roman 2018[644]	Systematic review is not relevant to review question or unclear PICO
Rothschild 2002[645]	Incorrect study design – non-randomised
Rowbottom 1998[646]	No validated outcome measures reported
Russell 2001[652]	Unpublished article
Russell 2017[651]	Systematic review is not relevant to review question or unclear PICO
Sabes-figuera 2012[654]	Not review population – no diagnosis of ME/CFS
Sandler 2016[657]	Incorrect interventions. One-off exercise challenges; not a therapeutic study.
Santaella 2004[658]	No relevant outcomes
Sathyapalan 2010[661]	No usable outcomes data – results reported as medians
Severens 2004[671]	HE analysis of excluded study (Prins 2001)
Sharpe 1998[677]	Article not in English
Sharpe 1998[674]	Incorrect study design – non-systematic review
Sharpe 2017[675]	Incorrect study design – non-systematic review
Shu 2016[680]	No usable outcome data – results only reported graphically
Smith 2003[686]	Incorrect interventions – chemical exposure to test response
Smith 2015[684]	Systematic review is not relevant to review question or unclear PICO
Stevens 1999[702]	Not available – thesis
Stoll 2017[705]	Systematic review is not relevant to review question or unclear PICO
Strang 2002[708]	Not available – thesis
Stubhaug 2008[714]	Pharma vs. non pharma interventions; considered in pharma review
Stulemeijer 2004[715]	Citation only
Sung 2020 [719]	Not review population – no diagnosis of ME/CFS
Taylor 2005[735]	Systematic review is not relevant to review question or unclear PICO
Taylor 2006[733]	Systematic review is not relevant to review question or unclear PICO
Teitelbaum 1999[736]	Abstract only
Teitelbaum 2001[737]	Not guideline condition
Tian 2015[759]	Article not in English
Toussaint 2012[763]	Not review population – fibromyalgia, chronic fatigue and/or CFS

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Study	Exclusion reason
Tummers 2010[768]	Incorrect study design – non-randomised; participants from intervention and control groups in Knoop 2008 decided whether they wanted to go on to receive CBT, results of CBT were compared between original groups
Van Cauwenbergh 2012[779]	Systematic review is not relevant to review question or unclear PICO
Van den Putte 2007[781]	Citation only
Van der Schaaf 2015[783]	Study protocol
Van Geelen 2011[786]	Inappropriate comparison – compared different intensities of the same intervention
Van Hoof 2003[787]	Incorrect study design – non-randomised
Vermeulen 2004[796]	Inappropriate comparison – compares different types of the same treatment
Viner 2004[800]	Incorrect study design – non-randomised
Vink 2019[802]	Reanalysis of a Cochrane review
Vos-Vromans 2009[806]	Citation only
Walach 2002[810]	Not review population – mix of CFS, chronic idiopathic fatigue, and multiple chemical sensitivity
Walach 2008[811]	Unclear population – study protocol specifies population were CFS/ICF/multiple chemical sensitivity, but study only mentions CFS
Wallman 2005[814]	No useable outcome data
Wang 2008[824]	Systematic review is not relevant to review question or unclear PICO
Wang 2009[820]	Article not in English
Wang 2009[821]	Article not in English
Wang 2009[819]	Inappropriate comparison – compares different types of the same treatment, massage therapy
Wang 2009[822]	Article not in English
Wang 2014[825]	Systematic review is not relevant to review question or unclear PICO
Wang 2017[823]	Systematic review is not relevant to review question or unclear PICO
Warren 1999[830]	No usable outcome data – results reported only as medians
Wearden 1996[833]	Citation only
Wearden 2007[832]	Citation only
Weatherley-Jones 2001[839]	Citation only
Wessely 1999[842]	Citation only
Wessely 2000[843]	Citation only
White 2012[845]	Citation only
White 2012[844]	Citation only
White 2013[846]	No relevant outcomes – number in each group meeting author defined criteria for recovery
Whitehead 2002[851]	Incorrect interventions – intervention for GPs
Whiting 2001[853]	Systematic review is not relevant to review question or unclear PICO
Wiborg 2010[855]	Reanalysis of previous RCTs
Williams 2002[860]	Pharma vs non-pharma; considered in pharma review

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Study	Exclusion reason
Worm-Smeitink 2019[871]	Inappropriate comparison – trial compares three different methods of delivering the same CBT protocol
Worm-Smeitink 2019[873]	Email (ethical approval)
Xu 2012[875]	Article not in English
Xu 2019[876]	Article not in English
Xu 2019[877]	Article not in English
Yiu 2007[878]	Article not in English
Yuemei 2006[879]	No validated outcome measures reported
Zhang 2009[887]	Article not in English
Zhang 2009[884]	Article not in English
Zhang 2011[883]	Article not in English
Zhang 2016[885]	Article not in English
Zhang 2019[882]	Systematic review is not relevant to review question or unclear PICO
Zhong 2016[889]	Article not in English
Zhu 2008[890]	Article not in English

J.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 64: Studies excluded from the health economic review

Reference	Reason for exclusion
Scheeres 2008[663]	Rated as having 'very serious limitations' due to being based on a before and after comparison in a single cohort.
Severens 2004[671]	Rated as 'not applicable' due to some of the the patients (proportion unknown) having idiopathic chronic fatigue (ME/CFS).

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Appendix K MIDs for continuous outcomes

Table 65: MID for continuous outcomes (0.5 x SD): Self-management versus Relaxation: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 sub scales) - Physical functioning Scale from: 0 to 100.	10.23
Quality of life (SF36 sub scales) - Role physical Scale from: 0 to 100.	9.3
Quality of life (SF36 sub scales) - Bodily pain Scale from: 0 to 100.	9.65
Quality of life (SF36 sub scales) - General health Scale from: 0 to 100.	10.65
Quality of life (SF36 sub scales) - Vitality Scale from: 0 to 100.	5.9
Quality of life (SF36 sub scales) - Social functioning Scale from: 0 to 100.	9.93
Quality of life (SF36 sub scales) - Role emotional Scale from: 0 to 100.	17.83
Quality of life (SF36 sub scales) - Mental health Scale from: 0 to 100.	8.63
Physical function (Canadian Occupational Performance Measure) - Performance Scale from: 1 to 10.	0.73
Physical function (Canadian Occupational Performance Measure) - Satisfaction Scale from: 1 to 10.	0.98

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Table 66: MID for continuous outcomes (0.5 x SD): Self-management (programme) versus Usual care: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36) - Mental component Scale from: 0 to 100.	5.2
Quality of life (SF36) - Physical component Scale from: 0 to 100.	3.5
Fatigue (Fatigue Severity Scale) Scale from: 9 to 63.	2.45

Table 67: MID for continuous outcomes (0.5 x SD): Self-management (adaptive pacing therapy) versus usual care: adults, severity mixed or unclear

Outcomes	MID
Quality of life (EQ5D) Scale from: -0.594 to 1.	0.14
Fatigue/fatigability (Chalder fatigue scale) Scale from: 0 to 33.	1.9
Physical functioning (SF36 physical function) Scale from: 0 to 100.	8.08
Psychological status (HADS anxiety) Scale from: 0 to 21.	2.13
Psychological status (HADS depression) Scale from: 0 to 21.	1.95
Pain (numeric rating scale) - muscle pain Scale from: 0 to 4.	0.67
Pain (numeric rating scale) - joint pain Scale from: 0 to 4.	0.74

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Outcomes	MID
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	2.48
Return to work (Work and social adjustment scale) Scale from: 0 to 40.	3.2
Exercise performance measure (6 minute walk test)	46.25

Table 68: MID for continuous outcomes (0.5 x SD): Self-management (programme) versus Usual care: severe; adults

Outcomes	MID
Fatigue (fatigue severity scale) Scale from:	0.25
Physical functioning (SF36 physical function) Scale from: 0 to 100.	10.05
Psychological status (Beck depression inventory) Scale from: 0 to 63.	5.34
Psychological status (Beck anxiety inventory) Scale from: 0 to 63.	5.17

Table 69: MID for continuous outcomes (0.5 x SD): Self-management (pacing) versus Stairway to health programme: severe; age mixed or unclear

Outcomes	MID
Quality of life (Child Health Questionnaire) Scale from: 1 to 5.	0.48

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Outcomes	MID
General symptom scales (Young person functional ability scale) Scale from: 0 to 100.	10.25
Fatigue (Chalder fatigue scale) Scale from: 0 to 42.	3.84
Psychological status (Birleson depression scale) Scale from: 0 to 36.	2.8
Psychological status (Hospital anxiety and depression scale - anxiety) Scale from: 0 to 21.	1.82
Return to school/work (% school attendance) Scale from: 0 to 100.	17.71

Table 70: MID for continuous outcomes (0.5 x SD): CBT versus usual care: adults, severity mixed or unclear

Outcomes	MID
Quality of life (EQ5D) - individual face-to-face CBT Scale from: -0.594 to 1.	0.13
Quality of life: SF-36 mental score - group based CBT SF-36 mental score. Pooled 6 and 12 months data. Scale from: 1 to 100.	5.55
Quality of life: SF-36 physical score - group based CBT SF-36 physical score. Pooled 6 and 12 months data. Scale from: 0 to 100.	4.22
Quality of life: Health status - group based CBT Health status (HUI3). Pooled 6 and 12 month data. Scale from: -0.36 to 1.	0.14
General symptom scales: Sickness Impact profile 8 (SIP8) - web/written CBT Scale from: 0 to 5799.	291.18
General symptom scales: sickness Impact profile 8 - group-based CBT Scale from: 0 to 5799.	246.5

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Outcomes	MID
Fatigue/fatigability (Checklist Individual strength - fatigue severity) - web/written CBT Scale from: 8 to 56.	2.65
Fatigue/fatigability (Checklist Individual strength - fatigue severity) - group-based CBT Scale from: 8 to 56.	2.38
Fatigue/fatigability (Chalder Fatigue Questionnaire) - web/written CBT Scale from: 0 to 33	2.6
Fatigue/fatigability (Chalder Fatigue Questionnaire) - group-based CBT Pooled 6 and 12 month data. Scale from: 0 to 33.	3.35
Fatigue/fatigability (Chalder fatigue questionnaire) - individual face-to-face CBT Scale from: 0 to 33.	1.83
Fatigue (fatigue severity 0-10 scale) - change scores - face-to-face CBT Scale from: 0 to 10.	0.85
Physical functioning (SF36 physical functioning sub-scale) - web/written CBT Scale from: 0 to 100.	10.38
Physical functioning (SF36 physical functioning sub-scale) - group-based CBT Scale from: 0 to 100.	9.7
Physical functioning (SF-36 physical functioning sub-scale) - individual face-to-face CBT Scale from: 0 to 100.	7.68
Cognitive function (total words recalled) - group-based CBT Pooled 6 and 12 months data	1.93
Cognitive function (correct words) - group-based CBT Pooled 6 and 12 months data	1.82
Cognitive function (reaction time) - group-based CBT Pooled 6 and 12 months data	48.7
Psychological status (Symptom Checklist 90 - psychological distress) - web/written CBT Scale from: 90 to 450.	17.94
Psychological status (Symptom Checklist 90 - psychological distress) - group-based CBT Scale from: 90 to 450.	18.9

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Outcomes	MID
Psychological status (Brief Symptom Inventory - psychological distress) - change scores - web/written CBT	0.31
Psychological status (HADS anxiety) - group-based CBT Pooled 6 and 12 months data. Scale from: 0 to 21.	2.03
Psychological status (HADS anxiety) - individual face-to-face CBT Scale from: 0 to 21.	2.15
Psychological status (HADS depression) - group-based CBT Pooled 6 and 12 months. Scale from: 0 to 21.	1.76
Psychological status (HADS depression) - individual face-to-face CBT Scale from: 0 to 21.	1.83
Psychological status (General health questionnaire) - group-based CBT Pooled 6 and 12 months. Scale from: 0 to 36.	3.43
Pain (joint pain numeric rating scale) - individual face-to-face CBT Scale from: 0 to 4.	0.74
Pain (muscle pain numeric rating scale) - individual face-to-face CBT Scale from: 0 to 4.	0.67
Sleep quality (Jenkins sleep scale) - individual face-to-face CBT Scale from: 0 to 20.	2.48
Activity levels (Actigraphy mean score) - web/written CBT	8.96
Activity levels (Number of days in bed per week) - change scores - individual face-to-face CBT	0.88
Activity levels (Percentage interference with activities) - change scores - individual face-to-face CBT Scale from: 0 to 100.	7
Return to school or work (Work and Social Adjustment Scale) - web/written CBT Scale from: 0 to 40.	4.71
Return to school or work (Work and social adjustment scale) - individual face-to-face CBT Scale from: 0 to 40.	3.23

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Outcomes	MID
Exercise performance measure (Normal walking speed) - group-based CBT Pooled 6 and 12 months data	2.21
Exercise performance measure (Shuttles walked) - group-based CBT Pooled 6 and 12 months data	0.27
Exercise performance measure (6 min walk test) - individual face-to-face CBT	49.5
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT Pooled 6 and 12 month data. Scale from: 0 to 10.	0.14

Table 71: MID for continuous outcomes (0.5 x SD): Group-based cognitive behavioural stress management versus psychoeducation: adults, severity mixed or unclear

Outcomes	MID
Quality of life: QOLI Quality of Life Inventory (QOLI) raw score	0.84
General symptom scales CDC Symptom Inventory. Scale from: 0 to 8.	0.18
Psychological status (Profile of Mood States - total mood disturbance)	14.79
Psychological status (Perceived Stress Scale) Scale from: 0 to 40.	4.02

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Table 72: MID for continuous outcomes (0.5 x SD): CBT (group-based) versus education and support group: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 mental) Pooled 6 and 12 month data. Scale from: 0 to 100.	5.73
Quality of life (SF36 physical) Pooled 6 and 12 month data. Scale from: 0 to 100.	3.71
Quality of life (Health status (HUI3)) Pooled 6 and 12 month data. Scale from: -0.36 to 1.	0.15
Fatigue (Chalder fatigue score) Pooled 6 and 12 month data. Scale from: 0 to 33.	3.13
Cognitive function (total words recalled) Pooled 6 and 12 month data.	1.85
Cognitive function (correct words) Pooled 6 and 12 month data.	1.8
Cognitive function (reaction time) Pooled 6 and 12 month data.	54.6
Psychological status (HADS anxiety) Pooled 6 and 12 month data. Scale from: 0 to 21.	2.07
Psychological status (HADS depression) Pooled 6 and 12 month data. Scale from: 0 to 21.	1.88
Psychological status (General health Questionnaire) Pooled 6 and 12 month data. Scale from: 0 to 36.	3.66
Exercise performance measure (Normal walking speed) Pooled 6 and 12 month data.	2.25
Exercise performance measure (Shuttles walked) Pooled 6 and 12 month data.	0.28
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT Pooled 6 and 12 month data. Scale from: 0 to 10.	0.18

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Table 73: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus multidisciplinary rehabilitation: adults, severity mixed or unclear

Outcomes	MID
Quality of life: SF-36 mental component summary SF36 mental component summary. Scale from: 0 to 100.	4.56
Quality of life: SF-36 physical component summary SF36 physical component summary. Scale from: 0 to 100.	3.93
General symptom scales Sickness Impact Profile 8. Scale from: 0 to 6160.	311.94
Fatigue (Checklist Individual Strength - fatigue severity) Scale from: 8 to 56.	2.54
Psychological status (Symptom Checklist) SCL-90. Scale from: 90 to 450.	18.57
Activity levels (Accelerometer) (Values divided by one decimal place)	2091.09

Table 74: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus relaxation: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Chalder Fatigue questionnaire) Scale from: 0 to 11.	0.98
Fatigue (Fatigue problem rating) Scale from: 0 to 8.	0.53
Physical functioning (short form general health survey physical functioning scale) Scale from: 0 to 100.	11.5
Psychological status (Beck depression inventory) Scale from: 0 to 63.	3.33
Psychological status (General health questionnaire) Scale from: 0 to 12.	1.95

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Outcomes	MID
Return to school or work (Work and social adjustment scale) Scale from: 0 to 8.	0.63

Table 75: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus adaptive pacing therapy: adults, severity mixed or unclear

Outcomes	MID
Quality of life (EQ5D) Scale from: -0.594 to 1.	0.13
Fatigue (Chalder fatigue questionnaire) Scale from: 0 to 33.	1.93
Physical functioning (SF-36 physical function subscale) Scale from: 0 to 100.	8.05
Psychological status (HADS anxiety scale) Scale from: 0 to 21.	2.13
Psychological status (HADS depression scale) Scale from: 0 to 21.	1.9
Pain (muscle pain numeric rating scale) Scale from: 0 to 4.	0.71
Pain (joint pain numeric rating scale) Scale from: 0 to 4.	0.75
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	2.45
Return to school/work (Work and Social Adjustment Scale) Scale from: 0 to 40.	3.08
Exercise performance measure (6 min walk test)	88

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Table 76: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus GET: adults, severity mixed or unclear

Outcomes	MID
Quality of life (EQ5D) Scale from: -0.594 to 1.	0.13
Fatigue/fatigability (Chalder fatigue questionnaire) Scale from: 0 to 33.	1.88
Physical functioning (SF36 physical function) Scale from: 0 to 100.	7.68
Psychological status (HADS anxiety) Scale from: 0 to 21.	2.13
Psychological status (HADS depression) Scale from: 0 to 21.	1.83
Pain (numeric rating scale) - muscle pain Scale from: 0 to 4.	0.69
Pain (numeric rating scale) - joint pain Scale from: 0 to 4.	0.66
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	2.3
Return to school/work (Work and social adjustment scale) Scale from: 0 to 40.	3.13
Exercise performance measure (6 minute walk test)	43.25

Table 77: MID for continuous outcomes (0.5 x SD): CBT (group-based) + GET versus usual care: age and severity mixed or unclear

Outcomes	MID
Quality of life (SF36 emotional role) Scale from: 0 to 100.	22.62

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Outcomes	MID
Quality of life (SF36 general health) Scale from: 0 to 100.	7.85
Quality of life (SF36 physical role) Scale from: 0 to 100.	12.75
Quality of life (SF36 social function) Scale from: 0 to 100.	12.62
Quality of life (SF36 vitality) Scale from: 0 to 100.	7.53
Quality of life (SF36 physical functioning) Scale from: 0 to 100.	11.22
Quality of life (SF36 mental health) Scale from: 0 to 100.	10.93
Quality of life (SF36 bodily pain) Scale from: 0 to 100.	10.82
General symptom scales Stanford Health Assessment Questionnaire - global health status. Scale from: 0 to 10.	1.05
Physical functioning (Stanford Health Assessment Questionnaire) Scale from: 0 to 3.	0.36
Pain (Stanford Health Assessment Questionnaire - pain intensity) Scale from: 0 to 10.	1.24

Table 78: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus psychoeducation/pacing: severity and age mixed or unclear

Outcomes	MID
General symptom scales Strengths and Difficulties Questionnaire. Scale from: 0 to 40.	2.56

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Outcomes	MID
Fatigue/fatigability (Chalder Fatigue Scale) Scale from: 0 to 33.	2.59
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	12.67
Return to school or work (% school attendance over 2 weeks) Scale from: 0 to 100.	22.8
Return to school or work (Work and Social Adjustment Scale) Scale from: 0 to 40.	0.73

Table 79: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus waiting list: children & young people, severity mixed or unclear

Outcomes	MID
Fatigue (Checklist Individual Strength - fatigue severity sub scale) Scale from: 8 to 56.	2.05
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	8.38
Return to school or work (School attendance (hours attended/total hours))	19.38
Cognitive function (Checklist individual strength – concentration sub scale) (change scores)	6.7
Cognitive function (Reaction time tests – simple & choice) (change scores) – simple	32.3
Cognitive function (Reaction time tests – simple & choice) (change scores) – choice	25.8
Pain (Daily pain – 0-4 scale) (change scores)	1.1
Pain (Muscle pain & joint pain – 1-4 scale) – muscle pain	0.4
Pain (Muscle pain & joint pain – 1-4 scale) – joint pain	0.45

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Table 80: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus counselling: age and severity mixed or unclear

Outcomes	MID
Fatigue (Chalder fatigue scale) Scale from: 0 to 33.	4.2
Psychological status (Hospital anxiety and depression scale - anxiety) Scale from: 0 to 21.	2.5
Psychological status (Hospital anxiety and depression scale - depression) Scale from: 0 to 21.	2.1

Table 81: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus GET: age and severity mixed or unclear

Outcomes	MID
Fatigue (Chalder fatigue scale) Scale from: 0 to 33.	2.27

Table 82: MID for continuous outcomes (0.5 x SD): CBT (web/written) versus usual care: young people, severity mixed or unclear

Outcomes	MID
Fatigue/fatigability (Fatigue severity (CIS-20)) Scale from: 8 to 56.	2.25
Physical functioning (Child health questionnaire physical functioning) Scale from: 0 to 100.	8.85
Return to school or work (mean school attendance) Scale from: 0 to 100.	15.5

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Table 83: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) + biofeedback versus usual care: children, severity mixed or unclear

Outcomes	MID
Fatigue (Fatigue Assessment Scale %) Scale from: 0 to 100.	1.98
Return to school or work (School attendance hours/month)	6.93

Table 84: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus relaxation: adults, moderate severity

Outcomes	MID
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	8.58
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	0.34
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	13.53
Psychological status (Beck depression inventory) Scale from: 0 to 63.	4.57
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	4.12
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	1.27
Pain (Brief Pain Inventory - interference) Scale range: 0-10	1.53
Pain (Muscle pain numeric rating scale) Scale range: 0-100	13.3
Pain (Joint pain numeric rating scale)	19.3

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Outcomes	MID
Scale range: 0-100	
Exercise performance measure (6 minute walk)	148.33

Table 85: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus cognitive therapy: adults, moderate severity

Outcomes	MID
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	7.43
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	0.3
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	12.79
Psychological status (Beck depression inventory) Scale from: 0 to 63.	5.17
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	3.72
Exercise performance measure (6 minute walk)	170.57
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	1.13
Pain (Brief Pain Inventory - interference) Scale range: 0-10	1.55
Pain (Muscle pain numeric rating scale) Scale range: 0-100	15.1
Pain (Joint pain numeric rating scale) Scale range: 0-100	17.6

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Table 86: MID for continuous outcomes (0.5 x SD): CBT (individual face-to-face) versus anaerobic activity therapy: adults, moderate severity

Outcomes	MID
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	7.86
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	0.36
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	10.77
Psychological status (Beck depression inventory) Scale from: 0 to 63.	5.63
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	3.84
Exercise performance measure (6 minute walk)	144.44
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	1.22
Pain (Brief Pain Inventory - interference) Scale range: 0-10	1.64
Pain (Muscle pain numeric rating scale) Scale range: 0-100	15.9
Pain (Joint pain numeric rating scale) Scale range: 0-100	19.4

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Table 87: MID for continuous outcomes (0.5 x SD): Education and support groups versus usual care: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 physical) Pooled 6 and 12 month data. Scale from: 0 to 100.	3.68
Quality of life (SF36 mental) Pooled 6 and 12 month data. Scale from: 0 to 100.	5.65
Quality of life (Health status (HUI3)) Pooled 6 and 12 month data. Scale from: -0.36 to 1.	0.15
Fatigue (Chalder fatigue score) Pooled 6 and 12 month data. Scale from: 0 to 33.	3.16
Cognitive function (total words recalled) Pooled 6 and 12 month data.	1.92
Cognitive function (correct words) Pooled 6 and 12 month data.	1.83
Cognitive function (reaction time) Pooled 6 and 12 month data.	54.48
Psychological status (HADS anxiety) Pooled 6 and 12 month data. Scale from: 0 to 21.	2.18
Psychological status (HADS depression) Pooled 6 and 12 month data. Scale from: 0 to 21.	1.64
Psychological status (General health Questionnaire) Pooled 6 and 12 month data. Scale from: 0 to 36.	3.58
Exercise performance measure (Normal walking speed) Pooled 6 and 12 month data.	3.36
Exercise performance measure (Shuttles walked) Pooled 6 and 12 month data.	11.46
Exercise performance measure (Perceived fatigue - modified Borg scale) - group-based CBT Pooled 6 and 12 month data. Scale from: 0 to 10.	0.15

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Table 88: MID for continuous outcomes (0.5 x SD): Cognitive therapy versus relaxation: adults, moderate severity

Outcomes	MID
Quality of life (Quality of Life Scale) Scale from: 16 to 112.	8.5
Fatigue (Fatigue Severity Scale) Scale from: 1 to 7.	0.34
Physical functioning (SF36 physical functioning) Scale from: 0 to 100.	12.59
Psychological status (Beck depression inventory) Scale from: 0 to 63.	4.08
Psychological status (Beck Anxiety Inventory) Scale from: 0 to 63.	4.07
Exercise performance measure (6 minute walk)	170.52
Pain (Brief Pain Inventory - severity) Scale from: 0 to 10.	1.11
Pain (Brief Pain Inventory - interference) Scale range: 0-10	1.40
Pain (Muscle pain numeric rating scale) Scale range: 0-100	15.4
Pain (Joint pain numeric rating scale) Scale range: 0-100	14.8

Table 89: MID for continuous outcomes (0.5 x SD): Buddy/mentor programme versus Wait-list: adults, severity mixed or unclear

Outcomes	MID
Quality of life (Quality of Life Index) Scale from: 0-30	2.05

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Outcomes	MID
General Symptom Scales (Chronic Fatigue Syndrome Symptom Rating Form) Scale from: 0 to 100.	1.45
Fatigue (Fatigue Severity Scale) Scale from: 1 to 63.	1.83
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	10.75
Psychological Status (Perceived Stress Scale) Scale from: 0 to 16.	1.13
Psychological Status (CORE-E - Overall Resource Gain) Scale from: 0 to 518.	37.21
Psychological Status (CORE-E - Overall Resource Loss) Scale from: 0 to 518.	51.73

Table 90: MID for continuous outcomes (0.5 x SD): The Lightning Process and specialist medical care versus specialist medical care: moderate, age mixed or unclear

Outcomes	MID
Fatigue (Chalder Fatigue Scale) Scale from: 0 to 33.	2.1
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	10.08
Psychological Status (Spence Children's Anxiety Scale) Scale from: 0 to 114.	9.25
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	2.23
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	1.88

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Outcomes	MID
Pain (Visual Analogue Scale) Scale from: 0 to 100.	14.48
Return to School/Work (School/college attendance in the previous week)	0.85

Table 91: MID for continuous outcomes (0.5 x SD): Pragmatic rehabilitation versus Supportive listening: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Chalder Fatigue Scale 11-item) Scale from: 0 to 11.	0.54
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	9.23
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	2.47
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	2.04
Sleep Quality (Jenkin's Sleep Scale) Scale from: 0 to 20.	2.41

Table 92: MID for continuous outcomes (0.5 x SD): Pragmatic rehabilitation versus Usual care: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Chalder Fatigue Scale 11-item) Scale from: 0 to 11.	0.57

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Outcomes	MID
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	9.37
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	2.46
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	2.08
Sleep Quality (Jenkin's Sleep Scale) Scale from: 0 to 20.	2.46
Exercise Performance Measure (Step-Test) - Number of Steps Completed	1.98
Exercise Performance Measure (Step-Test) - Time Taken to Complete Steps	8.98
Exercise Performance Measure (Borg rating of perceived exertion) Scale from: 6 to 20.	1.33

Table 93: MID for continuous outcomes (0.5 x SD): Supportive listening versus Usual care: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Chalder Fatigue Scale 11-item) Scale from: 0 to 11.	0.55
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	9.67
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Anxiety Scale from: 0 to 21.	2.55
Psychological Status (Hospital Anxiety and Depression Scale sub scales) - Depression Scale from: 0 to 21.	2.08
Sleep Quality (Jenkin's Sleep Scale) Scale from: 0 to 20.	2.43

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Table 94: MID for continuous outcomes (0.5 x SD): Mindfulness based cognitive therapy versus Wait-list: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Chalder Fatigue Scale) SMD used as two different scales combined (0-33 and 0-42)	0.5 (SMD)
Physical Functioning (SF36 Physical Functioning) Scale from: 0 to 100.	11.58
Psychological Status (Hospital Anxiety and Depression scale sub scales) - Anxiety Scale from: 0 to 21.	2.43
Psychological Status (Hospital Anxiety and Depression scale sub scales) - Depression Scale from: 0 to 21.	2.25
Return to School/Work (Work and Social Adjustment Scale) Scale from: 0 to 40.	4.28

Table 95: MID for continuous outcomes (0.5 x SD): Focused group therapy versus Wait-list: adults, severity mixed or unclear

Outcomes	MID
Quality of Life (Gothenburg Quality of Life Scale) Scale from: 18 to 126.	6.88
Quality of life (Visual analogue scale) Scale from: 0 to 10	1

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Table 96: MID for continuous outcomes (0.5 x SD): Graded exercise therapy versus standard care: adults, severity mixed or unclear

Outcomes	MID
Quality of life (EQ5D) Scale from: -0.594 to 1.	0.14
Fatigue/fatigability (Chalder fatigue questionnaire) SMD used as two different scales combined (0-33 and 0-42)	0.5 (SMD) PEM subgroup analysis for MD: PEM subgroup: 3.6 Unclear PEM subgroup: 4.21
Fatigue/fatigability (Chalder fatigue questionnaire) at 134 weeks Scale from: 0 to 33.	1.85
Physical functioning (SF36 physical function) Scale from: 0 to 100.	11.3 PEM subgroup analysis: PEM subgroup: 11.2 Unclear PEM subgroup: 9.99
Physical functioning (SF36 physical function) at 134 weeks Scale from: 0 to 100.	7.7
Psychological status (Hospital Anxiety and Depression Scale - depression) Scale from: 0 to 21.	1.95 PEM subgroup analysis: PEM subgroup: 1.93 <95% PEM subgroup: 1.88
Psychological status (Hospital Anxiety and Depression Scale - anxiety) Scale from: 0 to 21.	2.25 PEM subgroup analysis: PEM subgroup: 2.35 <95% PEM subgroup: 2.13
Pain (numeric rating scale 0-4) - muscle pain Scale from: 0 to 4.	0.67

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Outcomes	MID
Pain (numeric rating scale 0-4) - joint pain Scale from: 0 to 4.	0.74
Sleep quality (Jenkins sleep scale) Scale from: 0 to 20.	2.33
Return to school/work (Work and Social Adjustment Scale) Scale from: 0 to 40.	3.62
Return to school/work (Work and social adjustment scale) Scale from: 0 to 40.	3.25
Exercise performance measure (6 minute walk)	45.5
Exercise performance measure (VO2 peak/aerobic capacity)	2.8
Exercise performance measure (Peak power)	16.5
Exercise performance measure (Elapsed exercise test time - cycle ergometer)	1.25
Exercise performance measure (VEpeak)	6.5
Exercise performance measure (perceived exertion – Borg scale)	0.73

Table 97: MID for continuous outcomes (0.5 x SD): Graded exercise therapy versus flexibility/relaxation treatment: adults, severity mixed or unclear

Outcomes	MID
Fatigue/fatigability (Chalder fatigue scale total) Scale from: 0 to 42.	3.18
Fatigue/fatigability (Chalder fatigue scale sub scales) - Mental Scale from: 0 to 21.	0.96
Fatigue/fatigability (Chalder fatigue scale sub scales) - Physical Scale from: 0 to 21.	1.79

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Outcomes	MID
Physical function (SF36 physical function) Scale from: 0 to 100.	10.2
Cognitive function (Stroop test) - 82 questions	10.72
Cognitive function (Stroop test) - 95 questions	17.59
Psychological status (Hospital Anxiety and Depression Scale - depression) Scale from: 0 to 21.	1.51
Psychological status (Hospital Anxiety and Depression Scale - anxiety) Scale from: 0 to 21.	1.93
Exercise performance measure (Treadmill walking test duration)	1.83
Exercise performance measure (VO2peak)	2.75

Table 98: MID for continuous outcomes (0.5 x SD): Graded exercise therapy versus heart rate variability biofeedback therapy: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 physical component) Scale from: 0 to 100.	6.1
Quality of life (SF36 mental component) Scale from: 0 to 100.	4.45
Fatigue/fatigability (Multidimensional Fatigue Inventory) Scale from: 20 to 100.	7.95
Psychological status (Patient Health Questionnaire-9)	1.55

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Table 99: MID for continuous outcomes (0.5 x SD): Graded exercise therapy versus adaptive pacing therapy: adults, severity mixed or unclear

Outcomes	MID
Quality of life (EQ5D) Scale from: -0.594 to 1.	0.13
Fatigue/fatigability (Chalder fatigue scale) Scale from: 0 to 33.	1.95
Physical functioning (SF36 physical function) Scale from: 0 to 100.	8.08
Psychological status (Hospital anxiety and depression scale - depression) Scale from: 0 to 21.	1.88
Psychological status (Hospital anxiety and depression scale - anxiety) Scale from: 0 to 21.	2.1
Pain (NRS 0-4) - muscle pain Scale from: 0 to 4.	0.71
Pain (NRS 0-4) - joint pain Scale from: 0 to 4.	0.75
Sleep quality (Jenkins sleep scale)	2.3
Return to school/work (Work and social adjustment scale)	3.1
Exercise performance measure (6 minute walk test)	44.25

Table 100: MID for continuous outcomes (0.5 x SD): Graded exercise therapy versus intermittent exercise: adults, severity mixed or unclear

Outcomes	MID
Exercise performance measure (VO2 peak/aerobic capacity)	2.5
Exercise performance measure (Peak power)	6.25

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Outcomes	MID
Exercise performance measure (Elapsed exercise test time - cycle ergometer)	1.25
Exercise performance measure (VEpeak)	6
Exercise performance measure (rated perceived exertion – modified Borg scale) Scale from 0 to 10	0.5

Table 101: MID for continuous outcomes (0.5 x SD): GET versus Activity diaries: age and severity mixed or unclear

Outcomes	MID
Fatigue (Chalder fatigue scale - change scores)	4.03
Psychological status (Hospital anxiety and depression scale - depression - change scores) Scale from: 0 to 21.	1.49
Exercise performance measure (VO2 peak - change scores)	2.53

Table 102: MID for continuous outcomes (0.5 x SD): GET versus Standard care: age and severity mixed or unclear

Outcomes	MID
Fatigue/fatigability (Chalder fatigue questionnaire 0-11 scale) Scale from: 0 to 11.	1.04
Physical functioning (SF36 physical function 10-30 scale) Scale from: 10 to 30.	2.23
Psychological status (Hospital Anxiety and Depression Scale - depression) Scale from: 0 to 21.	2.38

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Outcomes	MID
Psychological status (Hospital Anxiety and Depression Scale - anxiety) Scale from: 0 to 21.	2.38
Sleep quality (Sleep problem questionnaire) Scale from: 0 to 20.	2.83

Table 103: MID for continuous outcomes (0.5 x SD): Intermittent exercise versus standard care: adults, severity mixed or unclear

Outcomes	MID
Exercise performance measure (VO2 peak/aerobic capacity)	3.25
Exercise performance measure (Peak power)	11.75
Exercise performance measure (Elapsed exercise test time - cycle ergometer)	1.5
Exercise performance measure (VEpeak)	7
Exercise performance measure (rated perceived exertion – modified Borg scale) Scale from 0 to 10	0.5

Table 104: MID for continuous outcomes (0.5 x SD): Orthostatic training versus sham: adults, severity mixed or unclear

Outcomes	MID
Fatigue/fatigability (Fatigue Impact Scale)	12.63

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Table 105: MID for continuous outcomes (0.5 x SD): Qigong versus no treatment: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 sub scales) - change scores - Mental health Scale from: 0 to 100.	9
Quality of life (SF36 sub scales) - change scores - Vitality Scale from: 0 to 100.	8.5
Quality of life (SF36 sub scales) - change scores - Bodily pain Scale from: 0 to 100.	9
Quality of life (SF36 sub scales) - change scores - General health Scale from: 0 to 100.	7
Quality of life (SF36 sub scales) - change scores - Social functioning Scale from: 0 to 100.	12.5
Quality of life (SF36 sub scales) - change scores - Role emotional Scale from: 0 to 100.	29
Quality of life (SF36 sub scales) - change scores - Physical functioning Scale from: 0 to 100.	6.5
Quality of life (SF36 sub scales) - change scores - Role physical Scale from: 0 to 100.	10.5
Fatigue (Fatigue severity scale) Scale from: 9 to 63.	0.3
Exercise performance measure (VO2 max)	2.8
Exercise performance measure (Max workload)	12.5
Exercise performance measure (Borg scale – rated perceived exertion) Scale from: 6 to 20.	1.0

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Table 106: MID for continuous outcomes (0.5 x SD): Anaerobic activity therapy versus cognitive therapy: adults, moderate severity

Outcomes	MID
Quality of life (Quality of life scale) Scale from: 16 to 112.	7.78
Fatigue/fatigability (Fatigue severity scale) Scale from: 1 to 7.	0.36
Physical functioning (SF36 physical function) Scale from: 0 to 100.	9.84
Psychological status (Beck depression inventory) Scale from: 0 to 63.	5.15
Psychological status (Beck anxiety inventory) Scale from: 0 to 63.	3.78
Exercise performance measure (6 minute walk test)	166.63
Pain (Brief pain inventory - severity) Scale from: 0 to 10.	1.06
Pain (Brief Pain Inventory - interference) Scale range: 0-10	1.50
Pain (Muscle pain numeric rating scale) Scale range: 0-100	17.4
Pain (Joint pain numeric rating scale) Scale range: 0-100	17.3

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Table 107: MID for continuous outcomes (0.5 x SD): Anaerobic activity therapy versus relaxation techniques: adults, moderate severity

Outcomes	MID
Quality of life (Quality of life scale) Scale from: 16 to 112.	8.94
Physical functioning (SF36 physical function) Scale from: 0 to 100.	10.58
Fatigue/fatigability (Fatigue severity scale) Scale from: 1 to 7.	0.4
Psychological status (Beck depression inventory) Scale from: 0 to 63.	4.55
Psychological status (Beck anxiety inventory) Scale from: 0 to 63.	4.18
Exercise performance measure (6 minute walk test)	144.39
Pain (Brief pain inventory - severity) Scale from: 0 to 10.	1.19
Pain (Brief Pain Inventory - interference) Scale range: 0-10	1.49
Pain (Muscle pain numeric rating scale) Scale range: 0-100	15.6
Pain (Joint pain numeric rating scale) Scale range: 0-100	18.9

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Table 108: MID for continuous outcomes (0.5 x SD): Isometric yoga versus Usual care: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Chalder fatigue scale) Scale from: 0 to 42.	3.08

Table 109: MID for continuous outcomes (0.5 x SD): Music therapy and Traditional Chinese Medicine versus Traditional Chinese Medicine: age and severity mixed or unclear

Outcomes	MID
Fatigue (Fatigue Scale based on Chalder Fatigue Scale)	1.71
Psychological status (Hamilton depression scale) Scale from: 0 to 52.	1.5
Psychological status (Hamilton anxiety scale) Scale from: 0 to 56.	0.73

Table 110: MID for continuous outcomes (0.5 x SD): Homeopathy versus Placebo: adults, severity mixed or unclear

Outcomes	MID
Quality of life (Functional limitations profile subscales) - Physical dimension	7.25
Quality of life (Functional limitations profile subscales) - Psychosocial dimension	7.45
Fatigue (Fatigue impact scale subscales) - Cognitive dimension Scale from: 0 to 40.	4.25
Fatigue (Fatigue impact scale subscales) - Physical dimension Scale from: 0 to 40.	3.48

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Outcomes	MID
Fatigue (Fatigue impact scale subscales) - Social dimension Scale from: 0 to 40.	7.98
Fatigue (Multidimensional fatigue inventory subscales) - General fatigue Scale from: 4 to 20.	0.98
Fatigue (Multidimensional fatigue inventory subscales) - Physical fatigue Scale from: 4 to 20.	1.33
Fatigue (Multidimensional fatigue inventory subscales) - Mental fatigue Scale from: 4 to 20.	1.68
Fatigue (Multidimensional fatigue inventory subscales) - Reduced activity Scale from: 4 to 20.	1.73
Fatigue (Multidimensional fatigue inventory subscales) - Reduced motivation Scale from: 4 to 20.	1.9

Table 111: MID for continuous outcomes (0.5 x SD): Acupuncture versus Sham acupuncture: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF12 subscales) - Physical Scale from: 0 to 100.	4.26
Quality of life (SF12 subscales) - Mental Scale from: 0 to 100.	4.95
Fatigue (Chalder fatigue scale subscales - 14-item) - Physical fatigue	2.66
Fatigue (Chalder fatigue scale subscales - 14-item) - Mental fatigue	2.54
Psychological status (GHQ12) Scale from: 0 to 12.	2

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Table 112: MID for continuous outcomes (0.5 x SD): Abdominal tuina versus Acupuncture: adults, severity mixed or unclear

Outcomes	MID
Fatigue (fatigue scale 14) Scale from: 0 to 14.	0.75
Psychological status (self-rating anxiety scale) Scale from: 20 to 80.	1.7
Psychological status (Hamilton rating scale for depression)	1.33

Table 113: MID for continuous outcomes (0.5 x SD): Low sugar, low yeast diet versus Healthy eating (advice): adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 subscales) - General health Scale from: 0 to 100.	9.7
Quality of life (SF36 subscales) - Physical function Scale from: 0 to 100.	12.48
Quality of life (SF36 subscales) - Role function Scale from: 0 to 100.	9.8
Quality of life (SF36 subscales) - Role emotion Scale from: 0 to 100.	22.78
Quality of life (SF36 subscales) - Social function Scale from: 0 to 100.	12.93
Quality of life (SF36 subscales) - Body pain Scale from: 0 to 100.	12.4
Quality of life (SF36 subscales) - Vitality Scale from: 0 to 100.	8.3
Quality of life (SF36 subscales) - Mental health Scale from: 0 to 100.	9.23

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Outcomes	MID
Fatigue: Chalder fatigue scale (14-item) Scale from: 0 to 42.	3.15
Psychological status (Hospital anxiety and depression scale subscales) - Anxiety Scale from: 0 to 21.	2.33
Psychological status (Hospital anxiety and depression scale subscales) - Depression Scale from: 0 to 21.	1.83

Table 114: MID for continuous outcomes (0.5 x SD): Acclydine and amino acids versus Placebo: adults, severity mixed or unclear

Outcomes	MID
General symptom scales (Sickness impact profile-8) Scale from: 0 to 5799.	250.53
Fatigue (Checklist individual strength - fatigue severity subscale) Scale from: 8 to 56.	3.83
Activity levels (Actometer)	11.43

Table 115: MID for continuous outcomes (0.5 x SD): Polynutrient supplement versus Placebo: adults, severity mixed or unclear

Outcomes	MID
General symptom scales (Sickness impact profile-8) Scale from: 0 to 5799.	337.25
Fatigue (Checklist individual strength - fatigue subscale) Scale from: 8 to 56.	1.95

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Outcomes	MID
Activity levels (Actometer) Scale from: 0 to 300.	9.33

Table 116: MID for continuous outcomes (0.5 x SD): Aribinoxylane versus Placebo: adults, severity mixed or unclear

Outcomes	MID
Quality of life (WHOQOL-BREF subscales) - Physical wellbeing Scale from: 0 to 100.	7.93
Quality of life (WHOQOL-BREF subscales) - Psychological wellbeing Scale from: 0 to 100.	8.1
Quality of life (WHOQOL-BREF subscales) - Social wellbeing Scale from: 0 to 100.	10.8
Quality of life (WHOQOL-BREF subscales) - Environmental wellbeing Scale from: 0 to 100.	8.08
General symptom scales (Measure yourself medical outcomes profile 2) Scale from: 0 to 6.	0.6
Fatigue (Chalder fatigue scale 11-item) Scale from: 0 to 11.	1.85
Psychological status (Hospital anxiety and depression scale) - Anxiety Scale from: 0 to 21.	2.25
Psychological status (Hospital anxiety and depression scale) - Depression Scale from: 0 to 21.	2.2

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Table 117: MID for continuous outcomes (0.5 x SD): Vitamin D versus Placebo: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Piper fatigue scale)	0.78
Psychological status (Hospital anxiety and depression scale) - Anxiety Scale from: 0 to 21.	2.2
Psychological status (Hospital anxiety and depression scale) - Depression Scale from: 0 to 21.	2.3

Table 118: MID for continuous outcomes (0.5 x SD): Coenzyme Q10 and NADH versus Placebo: adults, severity mixed or unclear

Outcomes	MID
Fatigue (Fatigue Index Scale) Scale from: 0 to 160.	8.73
Pain (McGill pain questionnaire subscales) - Affective Scale from: 0 to 12.	1.43
Pain (McGill pain questionnaire subscales) - Sensory Scale from: 0 to 33.	2.58
Sleep quality (Global Pittsburgh sleep quality index) Scale from: 0 to 21.	1.65
Exercise performance measure (VO2 max)	1.9
Exercise performance measure (Max workload in km/h)	10.6
Exercise performance measure (Perceived exertion – Borg scale – change scores) Scale from: 6 to 20.	0.82

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Table 119: MID for continuous outcomes (0.5 x SD): Guanidinoacetic acid (GAA) versus Placebo: adults, severity mixed or unclear

Outcomes	MID
Quality of life (SF36 sub scales) - PCS Scale from: 0 to 100.	2.45
Quality of life (SF36 sub scales) - MCS Scale from: 0 to 100.	6.65
Fatigue (Multidimensional fatigue inventory sub scales) - General fatigue Scale from: 4 to 20.	0.75
Fatigue (Multidimensional fatigue inventory sub scales) - Physical fatigue Scale from: 4 to 20.	0.5
Fatigue (Multidimensional fatigue inventory sub scales) - Mental fatigue Scale from: 4 to 20.	0.65
Fatigue (Multidimensional fatigue inventory sub scales) - Reduced activity Scale from: 4 to 20.	0.8
Fatigue (Multidimensional fatigue inventory sub scales) - Reduced motivation Scale from: 4 to 20.	0.75
Pain (Visual analogue scale) - At rest Scale from: 0 to 10.	0.55
Pain (Visual analogue scale) - During activity Scale from: 0 to 10.	0.75

Table 120: MID for continuous outcomes (0.5 x SD): Ubiquinol-10 versus Placebo: adults, severity mixed or unclear

Outcomes	MID
Cognitive function (Uchida-Kraepelin psychodiagnostic test) - Number of responses	35.82
Cognitive function (Uchida-Kraepelin psychodiagnostic test) - Number of correct responses	36.4

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Table 121: MID for continuous outcomes (0.5 x SD): Myelophil versus placebo: adults, severity mixed or unclear

Outcomes	MID
Fatigue (numeric rating scale) Scale from: 0 to 99.	7.73
Fatigue (visual analogue scale change score) Scale from: 0 to 10.	0.875
Fatigue (fatigue severity scale change score) Scale from: 9 to 63.	4.83

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Appendix L Research recommendations

L.1.1 Research recommendation

The development of a core set of relevant health outcome measures for trials of treatments for ME/CFS and the symptom management of ME/CFS.

L.1.2 Why this is important

There is considerable controversy over the outcome measures used in trials of treatments for ME/CFS and symptom management of ME/CFS. Inconsistency in outcomes used and concerns over the validity of some outcome measures in an ME/CFS population makes it difficult to combine and compare results from different trials, limiting the ability to draw conclusions on the clinical and cost effectiveness of interventions. The development of a core outcome set will allow the direct comparison of treatments for ME/CFS and symptom management and shape and optimise ME/CFS trial design.

L.1.3 Rationale for research recommendation / Modified PICO

Research question	Population: Specialist ME/CFS healthcare professionals and researchers People with lived experience of ME/CFS in the UK., including children and young people, people with severe and very severe ME/CFS, people with ME/CFS with learning disabilities. Intervention: For use in all trials of interventions to treat or manage ME/CFS. Setting: For intended use in research and practice.
Importance to patients or the population	At present there is no agreed core outcome set for ME/CFS for use in trials in the clinical effectiveness of treatments for ME/CFS or management of symptoms. Without a standardised set of validated outcome measures trials cannot be combined in meta-analysis and treatments can not be directly compared to allow clinicians to evaluate their effectiveness.
Relevance to NICE guidance	High quality research in this area will reduce the heterogeneity of the evidence base and will inform the evidence base to support decision making for NICE recommendations in the area of treatment and symptom management of ME/CFS.
Relevance to the NHS	Stronger recommendations for the treatment of ME/CFS and symptom management will offer clinicians clearer guidance in providing care for people with ME/CFS.
National priorities	None
Current evidence base	Throughout the development of the guideline the heterogeneity of the outcomes in the evidence base was noted.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Phase 1: Systematic search to identify existing or ongoing studies on developing a core outcome set using the COMET online database and studies reporting on Patient Reported outcome measures (PROMS). Phase 2: Systematic review to evaluate current outcome measures used in trials, identifying the frequency of use of each outcome and validation data. In line with the four-step process for developing core outcome sets outlined in the COMET handbook, this is to initially identify and agree on potential outcomes, to define and determine how they will be measured. These should include family reported outcome measures as well as patient reported outcome measures

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	Phase 3: To reach consensus on which outcomes should be included in the core outcome set, their definition and measurement, a Delphi consensus technique of multiple rounds, involving specialists, research experts and people with lived experience of ME/CFS in the UK will be used.
Feasibility	The proposed research can be carried out on a realistic timescale and at a reasonable cost. The systematic review of evidence as well as the survey or questionnaire methodology likely to be used to establish consensus are not likely to involve additional costs. The number of existing studies can provide a wealth of information on potential outcomes while consensus on outcomes is likely to depend on the response rate of ME/CFS specialists, researchers and people with lived experience of ME/CFS.
Other comments	There is controversy over the use of subjective outcome measures in ME/CFS effectiveness research and this would address that issue.
Importance	High: the research is of interest and will fill existing evidence gaps.

L.1.4 Research recommendation

What is the clinical and cost effectiveness of self-monitoring strategies and technologies in guiding energy management?

L.1.5 Why this is important

Energy management (also can be described as pacing by people with ME/CFS) is a widely use self-management strategy in ME/CFS. Many people with ME/CFS report benefit from the use of self-monitoring aids or technologies to establish limits for energy management and then assist or guide their energy management. Advice offered on self- management is currently variable with many services simply signposting or providing general advice rather than providing specific instructions in self-monitoring strategies. This is as a result of limited low quality evidence regarding the benefits of self-monitoring strategies in ME/CFS symptom management. A randomised controlled study into the benefits of self-monitoring strategies and tools will add a meaningful contribution to the evidence base in the symptom management of ME/CFS. There is a need for high quality trials into the effectiveness and cost effectiveness of self-monitoring strategies for the management of ME/CFS.

L.1.6 Rationale for research recommendation / Modified PICO

PICO question	Population: Adults, children and young people who are diagnosed as having ME/CFS. Subgroups: Pregnant women, women in the post-natal period, Black, Asian and minority ethnic populations Intervention(s):Self-monitoring strategies and techniques/technologies (for example, diaries, step monitors, heart rate monitors, actigraphy). Comparison: No treatment / wait list control / usual care/Each other Outcome(s): Quality of life, Fatigue/fatigability, Physical functioning, Cognitive function, Sleep quality, Treatment-related adverse effects, Pain, Activity levels, Exercise performance measures Family reported outcome measures

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Importance to patients or the population	If self-monitoring strategies and techniques offer clinically important benefits when added to care, at a reasonable cost threshold then it may be an important modality to enhance clinical outcome in this patient group. If specific strategies and techniques can be identified this will support people with ME/CFS to establish their limits for energy management and then guide energy management... Increased understanding of optimal strategies will support health care professionals and people with ME/CFS to make informed choices and improve patient outcomes. If self-monitoring improves family reported outcomes this may be a low-cost way to decrease domestic stress for patients.
Relevance to NICE guidance	This research will determine the effectiveness and cost-effectiveness of self-management strategies and enable future guidelines to clearly recommend for or against the use of self-management strategies and if they are effective what ones to recommend.
Relevance to the NHS	A clear recommendation for self-management strategies will offer clinicians clearer guidance on the best care for establishing limits and then guiding energy management for people with ME/CFS.
National priorities	None
Current evidence base	There is limited low quality evidence (5 RCTs). The self-management programmes used activity pacing to support people to regulate and appropriately allocate their available energy levels. The delivery and the content of the interventions varied. Delivery of the programmes included training sessions, online booklets and videos. Diaries and step counters were used to monitor activity in two studies. Most of the evidence showed no clinical difference between self-management strategies and any of the comparison groups (usual care or relaxation).
Equality	The recommendation is unlikely to impact on equality issues. There could be implications for reasonable adjustments in educational and work environments.
Study design	Randomised controlled trial with corresponding economic analysis. Long term follow-up of at least 2 and 5 years.
Feasibility	The trial is feasible and should be straightforward to carry out.
Other comments	
Importance	Low: the research is of interest and will fill existing evidence gaps.

L.1.7 Research recommendation

What is the clinical and cost effectiveness of sleep management strategies in the management of ME/CFS?

L.1.8 Why this is important

Debilitating fatigue that is not substantially relieved by rest is a key feature of ME/CFS. Many people with ME/CFS also experience sleep disturbance, such as insomnia or hypersomnia. The use of sleep management strategies as part of the management of ME/CFS is

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widespread, however practice is variable with many services simply signposting or providing general advice rather than providing specific instructions in sleep management strategies. This is in the face of a lack of evidence regarding the benefits of sleep management strategies in ME/CFS symptom management.

There is therefore a need for high quality trials into the clinical and cost effectiveness of sleep management strategies for the management of ME/CFS. A randomised controlled study into the benefits of sleep management strategies can make a meaningful contribution to the evidence base in the symptom management of ME/CFS potentially leading to better health outcomes for people with ME/CFS.

L.1.9 Rationale for research recommendation / Modified PICO

PICO question	Population: Adults, children and young people who are diagnosed as having ME/CFS Subgroups: Pregnant women, women in the post-natal period, Black, Asian and minority ethnic populations Intervention(s): Sleep management strategies, for example • Day time naps • Wakeful rest (includes relaxation techniques, self-hypnotherapy, mindfulness) • Sleep hygiene (for example consistent sleep/wake times, bedtime routines, dark room, quiet in the bedroom, impact of electronic devices, no caffeine/alcohol) • On demand sleep (i.e. responding to sleep needs intuitively without either denying sleep, nor trying to enforce it at pre-determined times.) • Vitamins/supplements (e.g. magnesium, B vitamins) • Medications (e.g. melatonin, tricyclics, hypnotics) • Weighted blankets • Ambient temperature control • Herbal remedies, for example, Lavender pillow spray Comparison: No treatment / wait list control / usual care/Each other Outcome(s): Quality of life, Fatigue/fatigability, Physical functioning, Cognitive function, Sleep quality, Treatment-related adverse effects, Pain, Activity levels, Exercise performance measures
Importance to patients or the population	If sleep management strategies are shown to offer clinically important benefits to the management of symptoms for people with ME/CFS, at a reasonable cost threshold, then it may be an important modality to improve current practice and enhance clinical outcomes in this patient group. If specific techniques are identified to be effective, this can support people with ME/CFS to choose effective techniques of sleep management while an increased understanding of optimal strategies can help standardise care and improve patient outcomes.
Relevance to NICE guidance	This research can reduce the existing uncertainty regarding the clinical and cost-effectiveness of sleep management strategies and support decision making in the development of future recommendations.

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Relevance to the NHS	A clear recommendation for sleep management strategies will offer clinicians clearer guidance on best care for people with ME/CFS. Increased knowledge of sleep management strategies would improve and standardise care.
National priorities	None
Current evidence base	There is currently no evidence on the clinical and cost-effectiveness of sleep management strategies for ME/CFS.
Equality	The trial is unlikely to impact on equality issues. There could be implications for reasonable adjustments in educational and work environments.
Study design	Randomised controlled trial with corresponding economic analysis. Long term follow-up of at least 2 and 5 years.
Feasibility	The trial is feasible and should be straightforward to carry out. High interest of people with ME/CFS in the development of management strategies is likely to ensure the identification an adequate sample to enable the study.
Other comments	When considering the population, all severities of ME/CFS should be included where possible, including people with severe or very severe ME/CFS.
Importance	Low: the research is of interest and will fill existing evidence gaps.

L.1.10 Research recommendation

What is the clinical and cost effectiveness of dietary strategies in the management of ME/CFS?

L.1.11 Why this is important

The use of dietary strategies in ME/CFS management is widespread. Practice is variable with many services simply recommending or signposting rather than providing specific instructions in dietary strategies. Fad diets or restrictive diets are commonly tried by people with ME/CFS wanting to improve their symptoms. This is in the face of limited low quality evidence regarding the benefits of dietary strategies in ME/CFS symptom management. A randomised controlled study into the benefits of dietary strategies will add a meaningful contribution to the evidence base in the symptom management of ME/CFS. There is a need for high quality trials into the effectiveness and cost effectiveness of dietary strategies for the management of ME/CFS.

L.1.12 Rationale for research recommendation / Modified PICO

PICO question	Population: Adults, children and young people who are diagnosed as having ME/CFS Subgroups: Pregnant women, women in the post-natal period, Black, Asian and minority ethnic populations Intervention(s): Dietary strategies, for example: • healthy eating diet • impact of different food groups • small frequent meals • low FODMAP • electrolyte supplements • fluid balance

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	• ketogenic diet (or low carbohydrate diet) • low histamine diet • dietary supplements (e.g., vitamins and minerals) • alterations of the gut biome (e.g. probiotics/ prebiotics supplements, decreasing processed foods) • use of aids and adaptions to support food preparation Comparison: No treatment / wait list control / usual care/Each other Outcome(s): Quality of life, Fatigue/fatigability, Physical functioning, gastrointestinal symptoms, Cognitive function, Sleep quality, Treatment-related adverse effects, Pain, Activity levels, Exercise performance measures, feasibility and cost to the person with ME/CFS, Measurement of key nutritional pointers and blood samples for vitamin and trace elements
Importance to patients or the population	If dietary strategies offer clinically important benefits to the management of symptoms for people with ME/CFS when added to care, at a reasonable cost threshold then it may be an important modality to enhance clinical outcome in this patient group. If specific techniques can be identified this will support people with ME/CFS to decide what techniques to choose. This research has the potential to improve in current practice. Dietary strategies are used to support the management of ME/CFS and aim to improve quality of life. Increased understanding of optimal strategies will improve care and patient outcomes.
Relevance to NICE guidance	This research will reduce the existing uncertainty regarding the effectiveness and cost-effectiveness of dietary strategies and will support future decision making for recommendations.
Relevance to the NHS	A clear recommendation for dietary strategies will offer clinicians clearer guidance on best care for people with ME/CFS. Increased knowledge of dietary strategies would improve and standardise care.
National priorities	None
Current evidence base	There is limited evidence base in the review, one small study of low quality showed no clinically important difference between a low sugar, low yeast diet and healthy eating advice for the majority of the SF36 quality of life subscales, fatigue or psychological status and a clinical benefit of healthy eating advice for the bodily pain subscale on SF36 with uncertainty.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Randomised controlled trial with corresponding economic analysis. Long term follow-up of at least 2 and 5 years.
Feasibility	The trial is feasible and should be straightforward to carry out.
Other comments	
Importance	Low: the research is of interest and will fill existing evidence gaps.

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Appendices Experience of interventions

Appendix A Review protocols

Review protocol for experiences of people who have had interventions for ME/CFS

ID	Field	Content
	Scope	Management of ME/CFS
	Draft review question	There are questions on the clincal and cost effectivness of interventions but it has become clear that this scope needs a mixed methods approach exploring the experiences of people. This is a controversial research area and one of the criticisms is that the trials do not capture or reflect the breadth of expereinces of people with ME/CFS when interventions are implemented.
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	What are the experiences of people who have had interventions for ME/CFS?
2.	Review question	What are the experiences of people who have had interventions for ME/CFS?
3.	Objective	This is a controversial research area and one of the criticisms is that the trials do not capture or reflect the breadth of experiences of people with ME/CFS when interventions are implemented. This reviews aims to explore the experiences of people who have had interventions for ME/CFS.

4.	Searches	The following databases will be searched: • Embase • MEDLINE • CINAHL • PsychINFO Searches will be restricted by: • English language The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review
5.	Condition or domain being studied	ME / CFS
6.	Population	People who have had interventions for ME/CFS
7.	Intervention/Exposure/Test	Experiences of people that have had interventions for ME/CFS and the benefits and harms they experienced,

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8.	Comparator/Reference standard/Confounding factors	NA
9.	Types of study to be included	Qualitative studies (e.g. transcript data collected from focus groups / semi structured interviews) and qualitative data from surveys
10.	Other exclusion criteria	Exclusion:
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Themes emerging from qualitative data
13.	Secondary outcomes (important outcomes)	Not applicable
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract information from studies (see Developing NICE guidelines: the manual section 6.4). Additional qualitative studies will be added to the review until themes within the analysis become saturated; i.e. studies will only be included if they contribute towards

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		the development of existing themes or to the development of new themes. The point at which data saturation is reached will be noted within the review.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual: For this review the CASP qualitative checklist will be used to assess risk of bias of individual studies. A sample of 10% of the critical appraisals will be quality assured by a second reviewer. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	The synthesis of qualitative data will follow a thematic analysis approach. Information will be synthesised into main review findings. Results will be presented in a detailed narrative and in table format with summary statements of main review findings. GRADE CERQual will be used to synthesise the qualitative data and assess the certainty of evidence for each review finding.
17.	Analysis of sub-groups	Stratification: • Children/young people vs. adults • People with severe ME/ less severe ME (as defined by the studies) • Type of intervention
18.	Type and method of review	☐ Intervention ☐ Diagnostic

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		☐ Prognostic ☒ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/05/19		
22.	Anticipated completion date	01/03/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑

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		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** [Give development centre name] **5b Named contact e-mail** [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre:		

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		• Dr Kate Kelley [Guideline lead] • Ms Maria Smyth [Senior systematic reviewer] • Ms Melina Vasileiou [Systematic reviewer] • Dr Richard Clubbe [Systematic reviewer] • Dr Karin van Bart [Systematic reviewer] • Mr David Wonderling [Health economist] • Ms Agnes Cuyas [Information specialist] • Ms Kate Ashmore [Project manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10091
29.	Other registration details	N/A
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]

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31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: Notifying registered stakeholders of publication Publicising the guideline through NICE's newsletter and alerts Issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Patients experience, information, diverticular disease
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

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Appendix B Literature search strategies

This literature search strategy was used for the following review questions:

- What are the experiences of people who have had interventions for ME/CFS?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[534]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve.

Searches for patient views were run in Medline (OVID), Embase (OVID), CINAHL, and PsycINFO (ProQuest).

Table 122: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 23 June 2020	Exclusions
Embase (OVID)	1974 – 23 June 2020	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 6 of 12 CENTRAL to 2020 Issue 6 of 12	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 23 June 2020	None
PsycINFO (ProQuest)	Inception – 23 June 2020	Exclusions
Epistemonikos (The Epistemonikos Foundation)	Inception - 23 June 2020	None

Medline (Ovid) search terms

37.	Fatigue Syndrome, Chronic/
38.	chronic* fatigue*.ti,ab.
39.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
40.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
41.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
42.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
43.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
44.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
45.	((Post-exertional or postexertional) adj2 malaise).ti,ab.

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46.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
47.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
48.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
49.	xenotropic murine leukemia virus-related virus.ti,ab.
50.	effort syndrome*.ti,ab.
51.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
52.	or/1-15
53.	letter/
54.	editorial/
55.	news/
56.	exp historical article/
57.	Anecdotes as Topic/
58.	comment/
59.	case report/
60.	(letter or comment*).ti.
61.	or/17-24
62.	randomized controlled trial/ or random*.ti,ab.
63.	25 not 26
64.	animals/ not humans/
65.	exp Animals, Laboratory/
66.	exp Animal Experimentation/
67.	exp Models, Animal/
68.	exp Rodentia/
69.	(rat or rats or mouse or mice).ti.
70.	or/27-33
71.	16 not 34
72.	limit 35 to English language

Embase (Ovid) search terms

35.	chronic fatigue syndrome/
36.	chronic* fatigue*.ti,ab.
37.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
38.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
39.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
40.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
41.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
42.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
43.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
44.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
45.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.

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46.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
47.	xenotropic murine leukemia virus-related virus.ti,ab.
48.	effort syndrome*.ti,ab.
49.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
50.	or/1-15
51.	letter.pt. or letter/
52.	note.pt.
53.	editorial.pt.
54.	case report/ or case study/
55.	(letter or comment*).ti.
56.	or/17-21
57.	randomized controlled trial/ or random*.ti,ab.
58.	22 not 23
59.	animal/ not human/
60.	nonhuman/
61.	exp Animal Experiment/
62.	exp Experimental Animal/
63.	animal model/
64.	exp Rodent/
65.	(rat or rats or mouse or mice).ti.
66.	or/24-31
67.	16 not 32
68.	limit 33 to English language

Cochrane Library (Wiley) search terms

#18.	MeSH descriptor: [Fatigue Syndrome, Chronic] this term only
#19.	chronic* fatigue*:ti,ab
#20.	(fatigue* near/2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)):ti,ab
#21.	((myalgic or post infection* or postinfection*) near/1 (encephalomyelitis or encephalopathy)):ti,ab
#22.	((ME near/1 CFS) or (CFS near/1 ME) or CFIDS or PVFS):ti,ab
#23.	(Systemic Exertion Intolerance Disease or SEID):ti,ab
#24.	((CFS near/1 SEID) or (SEID near/1 CFS) or (ME near/1 CFS near/1 SEID) or (ME near/1 SEID) or (SEID near/1 ME)):ti,ab
#25.	(Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS)
#26.	((Post-exertional or postexertional) near/2 malaise):ti,ab
#27.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia):ti,ab
#28.	((atypical or simulating or resembling) near/1 poliomyelitis):ti,ab
#29.	((chronic epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis):ti,ab
#30.	xenotropic murine leukemia virus-related virus:ti,ab
#31.	effort syndrome*:ti,ab
#32.	((akureyri or iceland or tapanui or "royal free" or "royal free hospital") near/1 disease*):ti,ab
#33.	((yuppie or yuppy or tapanui) near flu):ti,ab

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#34.	(or #1-#16)

CINAHL (EBSCO) search terms

S17.	(MH "Fatigue Syndrome, Chronic")
S18.	chronic* fatigue*
S19.	(fatigue* n2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*))
S20.	((myalgic or post infection* or postinfection*) and (encephalomyelitis or encephalopathy))
S21.	((ME and CFS) or (CFS and ME) or CFIDS or PVFS)
S22.	(Systemic Exertion Intolerance Disease or SEID)
S23.	((CFS and SEID) or (SEID and CFS) or (ME and CFS and SEID) or (CFS and ME and SEID) or (ME and SEID) or (SEID and ME))
S24.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome) and (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion))
S25.	((Post-exertional or postexertional) n2 malaise)
S26.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia)
S27.	((atypical or simulating or resembling) and poliomyelitis)
S28.	(chronic epstein Barr virus or chronic mononucleosis)
S29.	xenotropic murine leukemia virus-related virus
S30.	effort syndrome*
S31.	(((akureyri or iceland or tapanui or royal free or royal free hospital) and disease*) or ((yuppie or yuppy or tapanui) and flu))
S32.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

PsycINFO (ProQuest) search terms

2.	((((chronic* fatigue*) OR (fatigue* NEAR2 (disorder* OR syndrome* OR post viral OR postviral OR immune dysfunction* OR post infection* OR postinfection*)) OR ((myalgic OR post infection* OR postinfection*) NEAR1 (encephalomyelitis OR encephalopathy)) OR ((ME NEAR1 CFS) OR (CFS NEAR1 ME) OR CFIDS OR PVFS) OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS NEAR1 SEID) OR (SEID NEAR1 CFS)) OR ((ME NEAR1 CFS NEAR1 SEID) OR (ME NEAR1 SEID) OR (SEID NEAR1 ME)) OR ((Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) NEAR6 (CFS OR chronic* fatigue* OR ME OR myalgic OR SEID OR systemic exertion)) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR ((atypical OR simulating OR resembling) NEAR1 poliomyelitis)) OR (((chronic NEAR2 epstein Barr virus) OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR ((akureyri OR iceland OR tapanui OR royal free OR royal free hospital) NEAR1 disease*) OR ((yuppie OR yuppy OR tapanui) NEAR1 flu) OR MAINSUBJECT.EXACT.EXPLODE("Chronic Fatigue Syndrome"))) AND (stype.exact("Scholarly Journals") AND la.exact("ENG") AND po.exact("Human") NOT (me.exact("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Clinical Trial" OR "Qualitative Study" OR "Prospective Study" OR "Followup Study" OR "Literature Review" OR "Retrospective Study" OR "Systematic Review" OR "Meta Analysis") AND po.exact("Human"))

Epistemonikos search terms

2.	(advanced_title_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND

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	SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))) OR advanced_abstract_en:((advanced_title_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)) OR advanced_abstract_en:((chronic* fatigue* syndrome*) OR (fatigue* syndrome* OR fatigue* disorder* OR postviral fatigue* OR post viral fatigue* OR fatigue* immune dysfunction OR post infection fatigue* OR postinfection fatigue*) OR (encephalomyelitis OR encephalopathy) OR ("ME/CFS" OR "CFS/ME" OR "CFIDS" OR "PVFS") OR (Systemic Exertion Intolerance Disease OR SEID) OR ((CFS AND SEID) OR (SEID AND CFS) OR (ME AND CFS AND SEID) OR (ME AND SEID) OR (SEID AND ME)) OR (Orthostatic intolerance OR postural orthostatic tachycardia syndrome OR postural tachycardia syndrome OR POTS) OR ((Post-exertional OR postexertional) AND malaise) OR (neurasthenic neuroses OR epidemic neuromyasthenia OR neurataxia OR neuroasthenia OR neurasthenia) OR (atypical poliomyelitis OR simulating poliomyelitis OR resembling poliomyelitis) OR (chronic epstein Barr virus OR CEBV OR CAEBV OR chronic mononucleosis) OR (xenotropic murine leukemia virus-related virus) OR (effort syndrome*) OR (akureyri OR iceland disease OR tapanui OR royal free disease) OR (yuppie flu OR yuppy flu OR tapanui flu)))))

B.2 Health economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to ME/CFS population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018), with no date restrictions. NHS EED and HTA databases are

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hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 123: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 June 2020	Exclusions Health economics studies
Embase	2014 –30 June 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

55.	Fatigue Syndrome, Chronic/
56.	chronic* fatigue*.ti,ab.
57.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
58.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
59.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
60.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
61.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
62.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
63.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
64.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.
65.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
66.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
67.	xenotropic murine leukemia virus-related virus.ti,ab.
68.	effort syndrome*.ti,ab.
69.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
70.	or/1-15
71.	letter/
72.	editorial/
73.	news/
74.	exp historical article/
75.	Anecdotes as Topic/
76.	comment/
77.	case report/
78.	(letter or comment*).ti.
79.	or/17-24
80.	randomized controlled trial/ or random*.ti,ab.

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81.	25 not 26
82.	animals/ not humans/
83.	exp Animals, Laboratory/
84.	exp Animal Experimentation/
85.	exp Models, Animal/
86.	exp Rodentia/
87.	(rat or rats or mouse or mice).ti.
88.	or/27-33
89.	16 not 34
90.	limit 35 to English language
91.	Economics/
92.	Value of life/
93.	exp "Costs and Cost Analysis"/
94.	exp Economics, Hospital/
95.	exp Economics, Medical/
96.	Economics, Nursing/
97.	Economics, Pharmaceutical/
98.	exp "Fees and Charges"/
99.	exp Budgets/
100.	budget*.ti,ab.
101.	cost*.ti.
102.	(economic* or pharmaco?economic*).ti.
103.	(price* or pricing*).ti,ab.
104.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
105.	(financ* or fee or fees).ti,ab.
106.	(value adj2 (money or monetary)).ti,ab.
107.	or/37-52
108.	36 and 53

Embase (Ovid) search terms

50.	chronic fatigue syndrome/
51.	chronic* fatigue*.ti,ab.
52.	(fatigue* adj2 (disorder* or syndrome* or post viral or postviral or immune dysfunction* or post infection* or postinfection*)).ti,ab.
53.	((myalgic or post infection* or postinfection*) adj (encephalomyelitis or encephalopathy)).ti,ab.
54.	((ME adj CFS) or (CFS adj ME) or CFIDS or PVFS).ti,ab.
55.	(Systemic Exertion Intolerance Disease or SEID).ti,ab.
56.	((CFS adj SEID) or (SEID adj CFS) or (ME adj CFS adj SEID) or (ME adj SEID) or (SEID adj ME)).ti,ab.
57.	((Orthostatic intolerance or postural orthostatic tachycardia syndrome or postural tachycardia syndrome or POTS) adj6 (CFS or chronic* fatigue* or ME or myalgic or SEID or systemic exertion)).ti,ab.
58.	((Post-exertional or postexertional) adj2 malaise).ti,ab.
59.	(neurasthenic neuroses or epidemic neuromyasthenia or neurataxia or neuroasthenia or neurasthenia).ti,ab.

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60.	((atypical or simulating or resembling) adj poliomyelitis).ti,ab.
61.	((chronic adj2 epstein Barr virus) or CEBV or CAEBV or chronic mononucleosis).ti,ab.
62.	xenotropic murine leukemia virus-related virus.ti,ab.
63.	effort syndrome*.ti,ab.
64.	(((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)).ti,ab.
65.	or/1-15
66.	letter.pt. or letter/
67.	note.pt.
68.	editorial.pt.
69.	case report/ or case study/
70.	(letter or comment*).ti.
71.	or/17-21
72.	randomized controlled trial/ or random*.ti,ab.
73.	22 not 23
74.	animal/ not human/
75.	nonhuman/
76.	exp Animal Experiment/
77.	exp Experimental Animal/
78.	animal model/
79.	exp Rodent/
80.	(rat or rats or mouse or mice).ti.
81.	or/24-31
82.	16 not 32
83.	limit 33 to English language
84.	health economics/
85.	exp economic evaluation/
86.	exp health care cost/
87.	exp fee/
88.	budget/
89.	funding/
90.	budget*.ti,ab.
91.	cost*.ti.
92.	(economic* or pharmaco?economic*).ti.
93.	(price* or pricing*).ti,ab.
94.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
95.	(financ* or fee or fees).ti,ab.
96.	(value adj2 (money or monetary)).ti,ab.
97.	or/35-47
98.	34 and 48

NHS EED and HTA (CRD) search terms

#15.	MeSH DESCRIPTOR Fatigue Syndrome, Chronic
#16.	(chronic fatigue or fatigue syndrome*)

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#17.	((myalgic adj (encephalomyelitis or encephalopathy)))
#18.	(((ME adj CFS) or (CFS adj ME)))
#19.	(post viral fatigue or post viral syndrome* or viral fatigue syndrome* or PVFS)
#20.	#1 OR #2 OR #3 OR #4 OR #5
#21.	(neurasthenic neuroses or epidemic neuromyasthenia or post infectious encephalomyelitis or neurataxia or neuroasthenia)
#22.	(((atypical or simulating or resembling) adj poliomyelitis))
#23.	(chronic epstein Barr virus or chronic mononucleosis)
#24.	(xenotropic murine leukemia virus-related virus)
#25.	(((chronic fatigue and immune dysfunction syndrome*) or cfids or chronic fatigue-fibromyalgia syndrome* or chronic fatigue disorder* or Systemic Exertion Intolerance Disease or SEID or effort syndrome or post infectious fatigue))
#26.	((((akureyri or iceland or tapanui or royal free or royal free hospital) adj disease*) or ((yuppie or yuppy or tapanui) adj flu)))
#27.	#7 OR #8 OR #9 OR #10 OR #11 OR #12
#28.	#6 or #13

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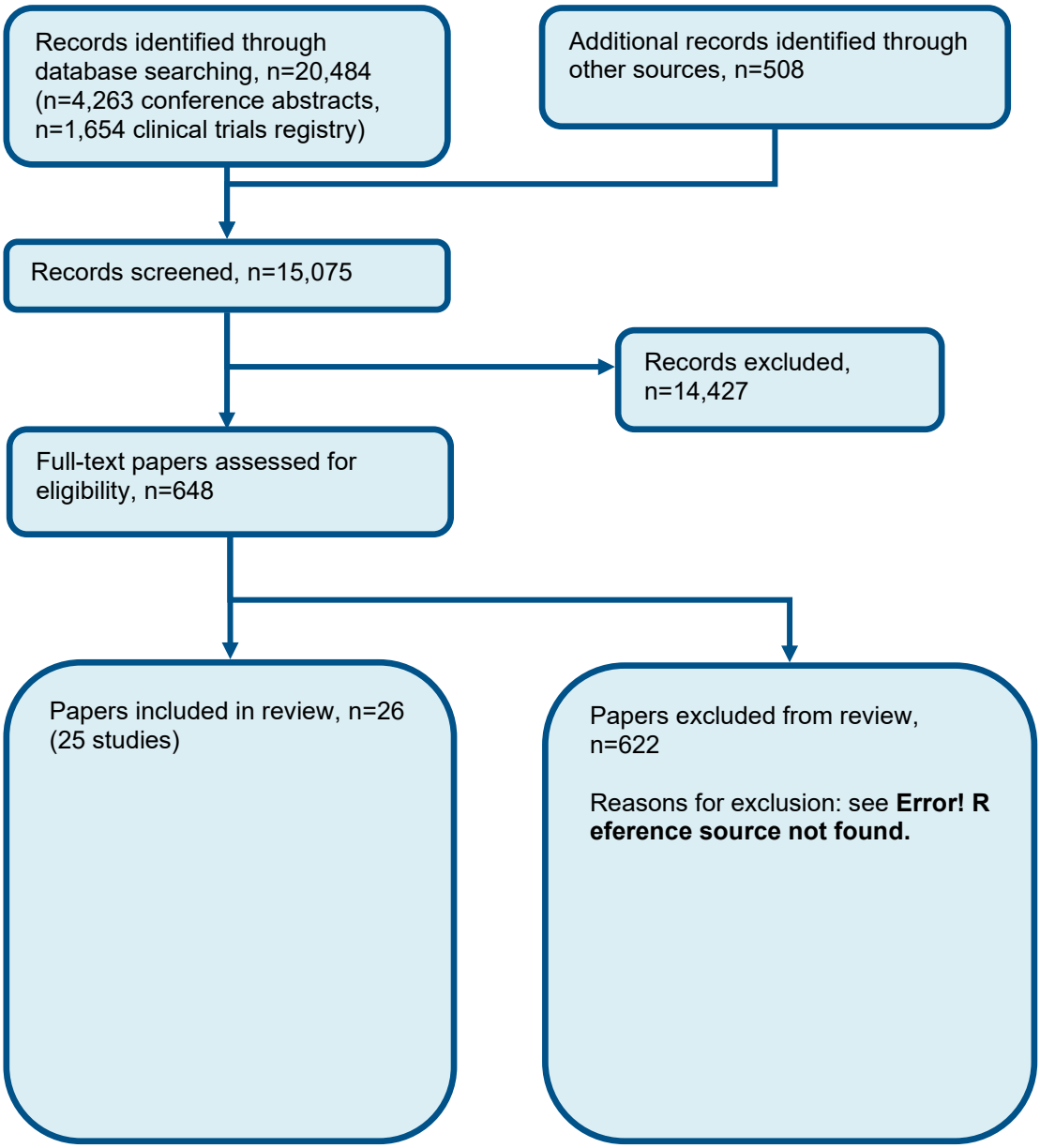
Appendix C Effectiveness evidence study selection

Figure 407: Flow chart of qualitative study selection for the review of experiences of interventions for ME/CFS



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Appendix D Qualitative evidence tables

Study	Bayliss 2016[58]
Aim	Following the development of an online training module for GPs, and an information pack and DVD for patients, this study explored the extent to which these resources can be implemented in routine primary care.
Intervention details	Resources for practitioners and patients to support the diagnosis and management of CFS/ME in primary care. This included an online training module for GPs (available on the Royal College for General Practice website) and a resource pack for patients. The resource pack included information sheets on how to manage the main symptoms of CFS/ME. These were designed to be discussed within a consultation, enabling the patient to work with their GP to prioritise and manage their symptoms. A DVD giving advice from CFS/ME specialists and case studies of patient and carer experiences was also provided for the patient and their families to watch at home. The resources were based on patient and practitioner need and were informed by 44 qualitative interviews with GPs, patients, carers and CFS/ME specialists. Patient and Public Involvement (PPI) was also central to the development of these resources and the research team included a patient co-applicant and a carer representative. Two patient involvement groups were also consulted quarterly to inform the design and content of the resource. Patient resource packs were delivered to all practices for use in consultation with new and existing CFS/ME patients. The pack was designed for the patient to prioritise their symptoms and thereby create their own 'personalised resource pack' in conjunction with the GP.
Population	Individuals with an existing diagnosis of CFS/ME, recruited from participating GP practices. Patients with other conditions, or other factors that may account for their fatigue were excluded. N=11; male/female 2/9; age range 27-74 years.
Setting	Participants' homes, UK.
Study design	Semi structured interviews with thematic analysis.
Methods and analysis	Patient interviews focused on their views on the CFS/ME patient resource and their experience with their GP before and after the practice had access to the online training. Interviews were digitally recorded and transcribed. Analysis was conducted in parallel with the interviews and was inductive, using components of thematic analysis. Thematic categories were identified in initial interviews and then explored in subsequent interviews. Main categories were compared across interviews and reintegrated into common themes. Interview transcripts were read, annotated, and categorised independently by researchers of different professional backgrounds and patient and carer research partners to increase reliability of the analysis. Open coding was used initially. It was agreed that theoretical saturation across the data sets was achieved when no new themes emerged during the final interviews.
Findings	**Validation**

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Study	Bayliss 2016[58]
	Patients with varying severity and time since diagnosis described how the provision of reliable evidence-based information meant that their GP was validating their CFS/ME. This enabled them to self-manage their condition.
	Knowledge and understanding
	Some patients reported a noticeable improvement in their GP's knowledge of CFS/ME following the training. The resources had a positive impact on the patient's understanding of CFS/ME. The DVD case studies were seen as particularly important in helping patients and carers to understand that others shared their experiences, and the format allowed those who found it difficult to read to access the information. As a result of this information some patients felt that they needed to visit their practice less frequently. Patients stated that the resource pack would be of greatest benefit to newly diagnosed patients. However, a number of patients who had the condition for a number of years reported that a comprehensive pack of information allowed them to consolidate their knowledge and sometimes learn something new. An evidence-based source of information was welcomed as there are currently issues with identifying reliable information on the internet.
	Impact on the friends, family and colleagues
	The resources were also reported to have had an impact on the friends, family and colleagues of the patients interviewed. In some cases, the provision of evidence-based information improved relationships and strengthened support networks.
Limitations and applicability of evidence	Minor methodological limitations due to unclear relationship between researcher and participants and no clear statement of findings. Only 53 % of patients who took part in this study reported receiving a copy of the information resource and for those who did receive it, it was often incomplete. All participants were provided with a copy prior to interview. No concerns regarding applicability. PEM reanalysis: moderate concerns over applicability due to participants being selected by GPs after excluding other conditions but it being unclear if selection was also based on PEM

Study	Beasant 2014[65]
Aim	To understand the experiences of adolescents and families in accessing and using a specialist service and to explore whether or not adolescents and their mothers value referral to a specialist service for young people with CFS/ME.
Intervention details	Participants were randomised to receive specialist medical care + Lightning Process or specialist medical care only. Specialist medical care + Lightning Process (LP) asked to read information about LP and complete an assessment form with their parents to identify their goals and describe what they had learnt. They then had a telephone call with an LP practitioner to discuss attending an LP course consisting of three 4-hour sessions on consecutive days run with groups of two to five young people. Each had a theory session with taught elements on the stress response, how the mind and body interact, and how thought processes can be

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Study	Beasant 2014[65]
	either helpful or negative. This was followed by group discussion where the language used was discussed and, in some cases, challenged, and where participants were encouraged to think about what they could take responsibility for and change. In the practical session, participants identified a goal they wished to achieve (such as standing for longer) and were given different cognitive (thinking) strategies before and while the goal was attempted. They were also asked to identify a goal to attempt at home. After the course, young people were offered at least two follow-up phone calls with an LP practitioner. Duration approx. 4.5 months. Concurrent medication/care: Specialist medical care: focused on improving sleep and using activity management to establish a baseline level of activity (school, exercise and social activity) which is then gradually increased. Sessions were delivered by a range of trained and supervised professionals including doctors, psychologists, physiotherapists and occupational therapists in family-based rehabilitation consultations. Follow-up sessions were either face to face or by telephone. The number and timing of the sessions were agreed with the family depending on each adolescent's needs and goals. Those with significant anxiety or low mood were offered additional CBT. Participants could choose to use physiotherapist-delivered graded exercise therapy, which provides detailed advice about exercise and focuses on an exercise programme rather than other activities.
Population	Adolescents taking part in the Specialist Medical Intervention and Lightning Evaluation (SMILE) study and their mothers. Participants were eligible for the SMILE study if they had been diagnosed with CFS/ME, were aged between 12 and 18 years and were mildly or moderately affected by the condition; that is, they were not house bound (NICE, 2007). Purposive sampling to ensure that interviews included a range of participants in terms of age, sex, socioeconomic circumstance and ethnicity as well as families from both intervention arms. N=12 adolescents; male/female 3/9; age mean (SD) 13.9 (1.6) years; illness duration median (IQR) 13 (9 to 18) months; 5 were interviewed post randomisation but before receiving the intervention, and 7 after the intervention. N=13 mothers; 5 mothers were interviewed at all three time points, 8 took part in one-off interviews: 4 post randomisation and 4 after their child received an intervention.
Setting	Participants' homes, UK
Study design	Semi structured interviews with thematic analysis
Methods and analysis	Families were interviewed at three possible time points: after initial assessment before randomisation, after randomisation before the intervention, and after the intervention. Adolescents with CFS/ME were interviewed once at one of these time points for not more than 20 min; parent interviews lasted for 20–60 min. A checklist of topics was used to ensure that similar areas were covered in each interview (experiences of the initial clinical assessment appointment, study participation and the interventions) but with sufficient flexibility to enable participants to raise topics of interest to them. Interviews were audio-recorded and transcribed. Data items were systematically assigned codes using the qualitative data organisation package NVivo and analysed thematically using techniques of constant comparison. Data analysis was an ongoing and iterative process, commencing soon after data collection started and informing further sampling and data collection. Two members of the research team analysed, 10% of the data independently to compare coding and enhance its reliability.

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Study	Beasant 2014[65]
Findings	**Recognition and progress – taking the next steps**
	The majority of mothers reported the initial assessment appointment as a positive experience. The service recognised and acknowledged the young person's condition, resulting in a sense of relief and reassurance. Mothers felt that symptoms were now being understood and they would receive help. Referral to a specialist service gave families access to an informative team of experts, for some a formal diagnosis, and for all a tailored, patient centred specialist medical intervention that had not been available earlier. This enabled positive change and steps towards a managed recovery. Some mothers felt that the CFS/ME service reinforced symptom management strategies that they had been trying to get their child to follow, and that they felt their child would be more likely to listen if techniques were legitimised by a health-care professional. Half the adolescents reported that specialist medical care was positive, as it enabled them to talk about their illness and gave guidance on how to manage their condition, which brought structure and a sense of normality back into their lives. However, half reported that, although specialist medical care resulted in better symptom management, accepting that for a time they must reduce activity levels and adopt a routine was challenging. A few mothers also noted that specialist medical care strategies had an impact on the whole family and could be difficult to integrate with their lifestyle.
	Dialogue opened between health-care professionals and education providers
	Mothers discussed the beneficial way in which the CFS/ME service opened channels of dialogue between health-care professionals and education providers in a variety of ways. A letter provided by the CFS/ME service confirming a diagnosis enabled mothers to legitimately take their child out of school, request funding for home schooling and more generally inform and gain support from teachers when managing reduced attendance.
Limitations and applicability of evidence	Minor methodological limitations due to unclear relationship between the researcher and participants and some findings supported by single quotes only. Moderate concerns regarding applicability due to study aim to understand the experiences of accessing as well as using a specialist service (some participants had not yet used the service) and unclear which intervention the findings relate to.

Study	Beaulieu 2000[66]
Aim	To examine multiple perspectives on stigmatization and legitimation of CFS.
Population	Health professionals including general practitioners, mental health professionals (one of whom was not a physician), infectious disease specialists, immunologists and rheumatologists, recruited following identification by people with CFS participating in the study. N=15; male/female 10/5; had been in practice from six to seventeen years and individually had seen from six to almost one hundred cases. People who were English-speaking and who had a diagnosis of CFS from a medical doctor, recruited from physicians' practices, support groups and identified by leaders of associations.

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Study	Beaulieu 2000[66]
	N=43; male/female 16/27; 26% were in school or working full or part time; mean age at onset was 34.2 years (range 15 to 58 years); people had been ill for an average of seven years. Significant others including friends, parents, spouses, adult children and a sibling, recruited following identification by people with CFS participating in the study. N=23; male/female not reported; 69% were working.
Setting	McGill University, Montreal
Study design	Qualitative interview study
Methods and analysis	Mixture of structured and semi structured questions related to approach to diagnosing, explaining and treating CFS, views on support groups and alternative therapies, whether thinking had changed over time, impressions of typical and atypical patients and challenges in dealing with sufferers (doctors); symptom experiences, the impact on roles and functioning, beliefs about cause, attempts to manage the illness through help seeking and treatment and reactions from health professionals (people with CFS); knowledge about sufferers' experiences, ideas about cause and treatments, how having someone close with CFS affected their lives (significant others). 78% of those who agreed to face to face interviews also consented to taping and tapes were transcribed. For telephone interviews and interviews in which people refused to be taped, notes of key words and phrases were taken. These notes were elaborated as soon as possible after the interviews. Interviews took place in people's homes, their offices, the researcher's office, or in neutral public places such as coffee shops or parks. A few doctors were interviewed by telephone. Interviews were analysed using thematic analysis. Transcripts of each interview were summarized according to the broadest content areas of questions. Summaries were then pooled according to categories and read and reread for recurring themes and variations in the first gross categories.
Findings	**Range of alternative therapies**
	Several sufferers tried a range of healers practicing Eastern and Western complementary therapies, including osteopaths, chiropractors, massage therapists, personal trainers, faith healers, homeopaths, naturopaths, herbalists, diet counsellors, hypnotists, colour therapists, iridologists, and energy healers. Some sufferers took up Yoga, Tai chi, macrobiotic and other diets, and primal screaming. Others tried reiki, shiatsu, zero balancing and craniosacral therapy. A few were treated with exotic machines such as the vibratoner and the Reumark3 machine.
	A holistic approach
	Sufferers were attracted to these diverse healers by a common element - a holistic approach. They found these healers were largely unconcerned with labels, but they tended to both mind and body whether they were offering a cure or symptom relief. Their approach of combining concrete action with empathy resonated with sufferers' ideas of what a health care practitioner should be. Alternative care practitioners also exposed sufferers to various philosophies and fresh perspectives on the source and meanings of illness. The most common new idea gleaned from many of these therapies was that energy blockage could be a source of illness.

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Study	Beaulieu 2000[66]
	Positive therapist approach
	Therapists' positive approaches gave sufferers hope that it was possible to overcome the illness. In some respects, they were similar to supportive doctors, but they had no authority to legitimate illness and grant certification that some sufferers required.
	Effectiveness
	Sufferers' evaluations of these therapies were mixed. Some were declared "absolutely useless", "not helpful" and "possibly harmful". Other sufferers experienced temporary effectiveness which reinforced their beliefs in these therapies.
	Follow up
	Several sufferers were impressed with the fact that unlike their regular doctors, these therapists called periodically to find out how they were managing.
Limitations and applicability of evidence	Serious methodological limitations due to recruitment strategy (HCPs referred by ME/CFS patients); unclear relationship between participants and researcher; data analysis (by a single researcher) and no clear statement of findings. Moderate concerns regarding applicability as main findings emerging are driven by the study's original aims to explore multiple perspectives on stigmatization and legitimation of CFS and limited detail on interventions received. PEM reanalysis: serious concerns regarding applicability due to existing reasons and it being unclear if participants experience PEM.

Study	Broadbent 2020[92]
Aim	To explore the experiences of participants in a short aquatic exercise programme for individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, and to gain insight into the perceived psychosocial benefits.
Intervention details	Five-week aquatic exercise intervention using a model of self-pacing or adapted pacing therapy (a person-centred approach to managing symptoms by using activity that is adapted to promote health and well-being; and where patients are active only within their symptom limits and energy limits). The intervention consisted of an initial session lasting 15–20 minutes, depending on each participant's physical ability and symptoms. To develop an atmosphere of comfort, support and social interaction, all participants were introduced to each other during the initial session and were encouraged to communicate and chat with fellow participants, instructors and assisting students. The sessions were kept as informal as possible. All participants were verbally encouraged throughout each session and constantly reminded that they were to self-pace and that they could rest if needed.

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Study	Broadbent 2020[92]
	Participants were shown how to use buoyancy vests if they wished to use these devices. All participants completed a variety of gentle intensity (RPE 2–5) range of motion, strengthening and aerobic water exercises that were performed to music. One of the researchers was the instructor and final-year exercise science students assisted participants in the pool with instruction and support if needed. The remaining four weeks of the intervention consisted of twice weekly aquatic sessions with two to three day's recovery between sessions. Sessions started at 15 minutes duration but gradually increased in time as, and if, participants were able to increase their exercise capacity. Participants were asked to self-pace and not to try and increase their time in the water, or intensity of exercise, if they were symptomatic.
Population	Participants were recruited from the local area by advertising through the media and university. Eligible patients had a prior medical diagnosis of ME/CFS, according to the updated International Canadian Consensus criteria or the 1994 Fukuda criteria. Inclusion criteria: between the ages of 18–80 years; a medical diagnosis of ME/CFS, post-viral fatigue syndrome or infectious mononucleosis; not participating in a physical activity programme or regular exercise; able to communicate in English; able to commit the time to participate in the research; able to provide informed consent. Exclusion criteria: any cardiovascular, pulmonary, metabolic, renal, endocrine, autoimmune, neurological illness, and any inflammatory condition, infectious disease or mental illness that made exercise participation a risk to participants; any diagnosed medical condition, other than ME/CFS, which might cause severe fatigue (e.g. cancer); any musculoskeletal injury that prevented exercise participation; being a non-swimmer; an allergy to chlorine or other pool chemicals; being pregnant. Participants who had diagnosed fibromyalgia as well as ME/CFS were not excluded. N=11; all females; 6 also diagnosed with Fibromyalgia; mean age 54.8 (12.4) years; duration of ME/CFS symptoms 17.0 (7.6) years; time since medical diagnosis 13.4 (6.2) years; other common co-conditions included depression/anxiety (n = 5), sleep disorders (n = 5), asthma/breathing difficulties (n = 7) and osteoarthritis (n = 6). Two of the cohort were unable participate in the final interview with the research team due to family and work commitments.
Setting	University laboratory, Australia.
Study design	Semi structured interviews with thematic analysis.
Methods and analysis	Participants returned to the laboratory in the week following the final aquatic session for post-intervention physical/functional assessments and for a semi-structured interview with two of the researchers. The interview consisted of nine open-ended questions which allowed further discussion and comments from each participant. Participants were reminded that they could answer all or some questions or not, and that any comments or feedback would remain confidential. All participants were encouraged to guide the discussion when answering the questions. Data collection continued until saturation was reached.

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Study	Broadbent 2020[92]
	The interview responses were transcribed by one of the researchers and later transferred to Excel spreadsheets for export to NVivo. The research questions were used as a framework to code the responses to the interview questions, including the changes in symptoms and additional comments. Main themes were identified in the first coding cycle and the coded text was further sorted into sub-themes in subsequent rounds of team discussion and analysis. Comparison of node content and coverage provided further information about associations between themes.
Findings	**Symptoms**
	The emerging trend for all participants was that approximately three weeks after commencing the programme, the severity of post-exercise symptoms declined. Aquatic exercises produced less fatigue than Tai Chi, yoga, stretching, cycling and running, and all participants found aquatic exercise less fatiguing. Other participants mentioned that water exercises didn't exacerbate symptoms, such as breathing difficulties and joint pain.
	Benefits
	The main benefits reported by participants were overall symptom improvement; enjoyment of the aquatic exercises; participants felt that they were better able to self-manage (symptoms, mastery of exercises); and the social benefits of group exercise with people with the same medical condition was extremely important. Other participants also emphasised that the exercise programme had social benefits and that participants had a commonality with their ME/CFS, in that they had similar ME/CFS stories and did not have to explain themselves to others. The quality of instruction and supervision (support, understanding, motivation), including the assisting students, was also mentioned by ten of the cohort. Additional responses outlined benefits such as increased fitness or use of muscles, enhanced breathing, better regulation of body temperature, and the engaging mixture and pacing of exercises. Two participants mentioned improved temperature regulation and fewer hot flushes, whilst another also reported improved cognitive symptoms such as 'better concentration, a clearer head'.
	Engagement and compliance
	The theme of engagement and compliance was strongly linked to both benefits and limitations. The physiological and psychosocial benefits of exercise participation resulted in good session attendance and adherence, with many participants reporting that their initial anxiety and fear of exercising had dissipated when they realised their symptoms were not exacerbated. The participants also reported that having an understanding session instructor made them feel comfortable in the aquatic and group environment, contributing to their enjoyment of the exercise and good attendance. Of the few sessions missed by three participants, one stated that a fibromyalgia symptom flare had stopped her attendance for one day, while another responded that she had been ill and symptomatic. Other reasons for missing sessions included commitments to work and children (school and medical appointments), a pre-booked holiday, and

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Study	Broadbent 2020[92]
	tiredness from doing 'too much the previous day, but not from the exercise'. The social benefits of group exercise also encouraged attendance and compliance, as did feelings of accomplishment and self-efficacy.
	Practical limitations
	Barriers to exercise participation included travel (driving for more than 15 minutes; community transport); initial anxiety about entering the water and possible onset of severe symptoms; and low energy levels. Several participants commented that driving was extremely tiring physically and mentally. Another participant was unable to drive and had to rely on community transport which was expensive and often difficult to arrange. Anxiety about exercise was an initial issue with all participants but non-exacerbation of symptoms appeared to be a key factor in anxiety reduction. There were other aspects of the study that some participants did not like including the time it took to get undressed and dressed, the energy needed to remove wet swimsuits and heart rate monitors, the discomfort of wearing a heart rate monitor (one participant only), and the possible need for a bit more space in the pool. Two participants commented that sessions could be longer or more frequent.
Limitations and applicability of evidence	Minor methodological limitations due to unclear relationship between researcher and participants (one of the researchers was the instructor but it is unclear whether this researcher was involved in interviews) and data analysis (not a lot of detail given on methodology). Moderate concerns regarding applicability due to all participants being female (findings may not be applicable to males). PEM reanalysis: serious concerns over applicability due to existing reasons and it being unclear if participants had PEM as it is not a compulsory feature in the Fukuda 1994 criteria and the number of those diagnosed using the International Canadian Consensus criteria cannot be determined.

Study	Cheshire 2020[154]
Aim	To explore patient experiences of Guided graded Exercise Self-help (GES) delivered as part of a randomised controlled trial (GETSET) for people with ME/CFS to answer the research question: 'What are the differences and similarities in treatment perceptions and experiences of GES among CFS/ME participants reporting an improvement compared with those reporting a deterioration in their condition?'
Intervention details	Guided graded Exercise Self-help Self-help booklet describing a 6-step programme of graded exercise self-management, based on the approach of GET developed for the PACE trial and NICE recommendations. Six steps: stabilising a daily routine, starting regular stretching, deciding on a physical activity goal and choosing a type of activity with which to start, setting a physical activity baseline, increasing the duration of physical activity and finally the intensity. If symptoms increased after an incremental change in activity, participants were advised to maintain

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Study	Cheshire 2020[154]
	activity at the same level until symptoms had settled, before considering another incremental increase. In the first 30 minute session (face-to-face, by Skype or by phone), a physiotherapist provided guidance on following the booklet and answered any questions. Up to 3 further 20 minute appointments by skype/telephone were offered over 8 weeks by 2 experienced physiotherapists who were trained to support participants in using the booklet, but explicitly told not to provide therapy. Physiotherapists inquired about progress, answered questions, with a focus on moving forward to the next step, recognised achievements and provided feedback, with the aim of increasing motivation and self-efficacy. A therapy leader trained the two physiotherapists until they were deemed competent and then provided regular individual supervision. Physiotherapists followed a manual and all participant guidance sessions were audio-recorded for supervision, feedback, and monitoring of treatment integrity. If a participant could not be contacted by telephone or Skype, an email was sent to re-engage them. Duration 8 weeks. Concurrent medication/care: Before randomisation, all patients had at least one specialist medical care consultation, delivered by doctors with specialist experience in chronic fatigue syndrome. SMC could involve prescriptions or advice regarding medication, as indicated for symptoms or comorbid conditions such as insomnia, pain, or depressive illness. Although not routinely scheduled during the trial, further SMC sessions were available after randomisation for patients who required it, but it was not a standardised intervention.
Population	People who had participated in the GES arm of the GETSET trial and had rated themselves as improved or deteriorated after the intervention (using clinical global impression of change scale); severely affected patients were not included in the trial. N=19 (n=9 reported feeling 'much better', n=10 reported feeling 'a little worse' – initial aim to recruit 10 reporting 'much better' or 'very much better' and 10 reporting 'much worse' or 'very much worse', but none reported feeling 'much worse' or 'very much worse', so inclusion criteria were expanded to include 'a little worse'); majority Caucasian (17/19); male/female 2/17; mean age (IQR) for 'much better' group 39 (21-54) years, for the 'a little worse group 43 (28-66) years; median (IQR) length of time since symptom onset for the 'much better' group 4 (3-5) years, for the 'a little worse' group 13 (8-21) years.
Setting	Interviews conducted by telephone (n=11), at patients' homes (n=6), at patients' place of work (n=1) and at the University (n=1); trial setting secondary care, UK.
Study design	Qualitative one-to-one interview study with thematic analysis.
Methods and analysis	Semi-structured interviews. Topics included before and after trial wellbeing, expectations of GES, barriers and facilitators to GES and any outside influences on the trial or GES participation. Interviews lasted between 13 and 80 minutes (mean 45 mins). Interviews were audiotaped, transcribed and returned to the participant for checking. Thematic analysis conducted by researchers independent of the implementation of the GETSET trial. Transcripts were analysed, a list of themes was compiled and examined by two researchers. The data were coded and explored using NVivo (qualitative data analysis software) to generate reports for each group for each theme, enabling a systematic comparison between the groups for each topic. Analysis and draft manuscript were critiqued and contributed to by the other authors, independent researchers and the patient representatives.
Findings	**Getting started and false starts**

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Study	Cheshire 2020[154]
	Most participants reported finding attempting to stabilise their routine, choosing their specific physical activity and setting their baseline level activity to be relatively straightforward. Two participants in the 'a little worse' group reported 'false starts' as they commenced their GES activity – one due to a physical reaction believed to be due to a pre-existing hip condition and was given medical advice to discontinue and the other due to major life events which left her too preoccupied to engage with GES. Regardless of group, the majority of participants reported that following the GES programme was 'hard work'.
	The 'indeterminate phase' of GES
	Two participants reported that they felt better immediately after exercise and this immediate positive feedback encouraged them to continue with the programme. However, during the first phase of the GES programme, most participants noticed no immediate difference in symptoms, or an exacerbation. For those who did begin to feel better, improvement was reported as remarkably incremental. When participants experienced a setback to their incremental progress, it could be experienced as particularly demoralising. Many GES participants had delayed gains and little or no short-term benefit, which resulted in them not knowing if GES was helping or hindering their condition. During this 'indeterminate phase', it was found to be difficult to maintain motivation, particularly when experiencing exacerbation of symptoms or when finding the programme hard work or boring. Those who avoided false starts were generally able to stick to their GES programmes through this phase and beyond.
	Competing commitments
	The flexibility and patient-centeredness of the GES programme supported participants to develop programmes that fitted into their lifestyle. However, participants described needing enough 'capacity' in their lives to experience an exacerbation of symptoms and for this not to interfere with essential life activities. GES worked best for people who had fewer commitments that interfered with GES, such as work, looking after children, housework, lifestyle changes, etc. If a supportive partner or workplace could relieve them of other commitments, they seemed better placed to benefit from GES. For some participants who were more physically disabled, having lower levels of functioning could create time and space to do GES as they only needed to find a small amount of time each day and they were sometimes in a situation where they had few other commitments due to lower functioning and so could focus on GES more fully. Higher functioning participants had more to do in their lives and reported more challenges in fitting GES in to busier lifestyles.
	Interfering symptoms and comorbid conditions
	Exacerbations of symptoms were reported as more debilitating in the 'a little worse' group, who had had ME/CFS for longer and half of them reported discontinuing GES activities for this reason. This group also reported more comorbid conditions such as joint hypermobility, fibromyalgia, irritable bowel syndrome, endometriosis, depression, arthritis, sciatica and asthma and greater interferences from these conditions when doing GES. One participant reported memory problems, which impacted her ability to undertake GES.
	Maintaining motivation
	A number of participants, particularly in the 'much better' group gave accounts revealing high levels of motivation to continue with GES. Factors influencing motivation and ability to undertake GES were:

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Study	Cheshire 2020[154]
	a) **The importance of guidance** - Approaches and attitudes taken by physiotherapists that were enthusiastic, gentle, understanding and patient centred (rather than prescriptive) generally facilitated participants' engagement with them and the GEs programme. b) **Features of the GES programme** – Some participants found the GES booklet helpful, whereas two others found it patronising, having the feel of marketing material or seemingly designed for participants with a higher level of functioning. They noted in particular that the statement suggesting that there should be no ill effects from GES was not accurate in their experience. Participants reported that being allowed to choose their own activities supported motivation. Some felt that the remit of GES was too narrow and that it needed a broader approach which included CBT, or took into account mental activity. c) **Participant beliefs and understanding of GES** – An understanding of the theory behind GES helped participants understand and engage in GES. For many, understanding was established when GES was explained at the beginning of the trial or from previous experience of GET. Those who had previously unsuccessfully tried GET, or attempted to increase activity levels without support found it useful to have an explanation for the possible failure of previous attempts and could motivate them to stick to their GES programme and do it 'correctly'. d) **Support from other people and therapies** – A number of participants in the 'much better' group reported use of GES being supported by other complementary therapies, counselling, CBT, self-help or peer support. Two participants had used complementary therapies during the trial, which they felt supported their recovery and gave them more energy, making it easier for them to engage with GES.
Limitations and applicability of evidence	No significant methodological limitations noted. No concerns about applicability.

Study	Dennison 2010[231]
Aim	To explore in detail adolescent patients' and their parents' experience of both family-focused CBT and psychoeducation for CFS. The study aimed to elicit participants' experiences in their own terms in order to better understand participants' expectations, therapy experiences and views regarding the effectiveness of their treatment.
Intervention details	Family focused CBT 13 x 1-h sessions of CBT every 2 weeks. Treatment protocol adapted from that used in a trial of CBT for CFS in adults (Deale et al. 1997), taking into account the specific needs of this age group. Particular emphasis placed on building a rapport with all members of the family and establishing a collaborative relationship. Involved encouraging the participant to achieve a balance between activity and rest; gradually increasing activities including home, social and school life; establishing a sleep routine; addressing beliefs such as fear regarding the relative benefits of activity and/or exercise, high self-expectations and all-or-nothing thinking; encouraging individuals within the family to express their own views about the illness and agreeing a way forward and paying attention to relapse prevention. The parent providing the majority of the care was supported as the adolescents became more independent. Homework assignments were negotiated with participants at each session. A treatment guide, Self Help for Chronic Fatigue Syndrome: A Guide for Young

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Study	Dennison 2010[231]
	People (Chalder & Husain, 2002), was given to the family. Therapists sought to maintain neutrality and acted as brokers in the not infrequent adolescent/parent disputes. Delivered by two trained and experienced cognitive behavioural psychotherapists. Duration 6 months. Concurrent medication/care: Close liaison with relevant school teachers and home tutors was initiated from the start of treatment and maintained throughout. Key issues for discussion were: endorsement of the reality of the condition, negotiating a graded return to school and for some reducing the number of subjects taken. In some cases, repeat years were negotiated. Anxieties about reintegrating with peer groups were addressed and some adolescents were supported in changing academic institutions altogether. In both groups the entire family was invited to the first session and the mother accompanied the child to every subsequent session. Other members of the family attended when they could. Psychoeducation 4 sessions over a 6-month period. Content similar to CBT, but mode of delivery was didactic. Involved discussion, information giving and problem solving but specific homework assignments and cognitive restructuring not included. Families were not given a manual. Therapists ensured adherence to protocol by working from a checklist that included the following. (a) Gave the message that untreated CFS in adolescents has a good prognosis. (b) Presented a model of CFS that distinguished predisposing, precipitating and maintaining factors. (c) Introduced the concept of symptom management – that the way we manage our physical symptoms can make a difference to the outcome. Physical illness analogies such as heart disease were used to increase likelihood of engagement. (d) Gave advice on pacing and consistency of activity and rest, in order to break the vicious circle of symptom lead behaviour. (e) Gave advice on sleep management. (f) Conveyed the message that hurt does not equal harm – increased symptoms do not mean more pathology. (g) Advised clients to gradually build up activity over a period of months. Duration 6 months. Concurrent medication/care: Close liaison with relevant school teachers and home tutors was initiated from the start of treatment and maintained throughout. Key issues for discussion were: endorsement of the reality of the condition, negotiating a graded return to school and for some reducing the number of subjects taken. In some cases, repeat years were negotiated. Anxieties about reintegrating with peer groups were addressed and some adolescents were supported in changing academic institutions altogether. In both groups the entire family was invited to the first session and the mother accompanied the child to every subsequent session. Other members of the family attended when they could.
Population	Young people and their parents who had participated in a randomised controlled trial comparing family focused CBT with psychoeducation. N=16 young people; all white British; male/female 6/10; mean age (range) 19.9 (16-24; 13-18 at the time of starting therapy) years; n=7 received CBT, n=9 received psychoeducation. N=16 parents; all white British; male/female 2/14; n=9 were involved in CBT, n=7 were involved in psychoeducation
Setting	Telephone based interview, UK
Study design	Qualitative interview study with thematic analysis.

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Study	Dennison 2010[231]
Methods and analysis	Telephone based semi-structured interviews by researchers who had not met the participants, nor been involved in their therapeutic management and who were blinded to the treatment allocation. Interviews consisted of a series of broad open-ended questions and non-directive prompts. Participants were encouraged to talk about the issues they personally considered important and departures were made from the schedule and subjects spontaneously raised by participants were probed further. Interviews typically lasted around 30 minutes (9.5 to 56 minutes). Interviews were tape recorded and transcribed. Thematic analysis conducted by researchers who were blinded to the treatment allocation. An initial coding manual was developed and was subsequently revised to incorporate more data as further transcripts became available. Coding was iterative and the method of constant comparison was used to ensure that themes were applied sensitively and as indicated by the data. The final coding manual was reviewed by other members of the research team. Researchers were then unblinded to treatment group and themes were examined in the context of treatment group.
Findings	**Relationship with the therapist**
	Most young people found the therapy sessions acceptable or even enjoyable; they were not as intimidating as expected. The therapist's personality and interpersonal skills were important. Often the young people did not perceive the sessions a formal therapy, rather they were just a 'chat'. Nearly all young people and parents emphasised that having somebody to talk to who was interested in and understood CFS was a key positive feature of therapy sessions. Recognition, validation and emotional support were almost always cited as important. These benefits were appreciated regardless of whether other aspects of the therapy were deemed useful.
	Session content
	For the majority of both young people and parents, the approach was deemed valuable. Techniques used in the sessions were typically described as 'common sense' and 'practical advice' often for the first time since the child had become ill. The behavioural aspects of the therapy emerged as being particularly valued and accepted by the young people who found these easy to 'latch on to'. Help with setting goals for physical activity and implementing sleep routines were frequently cited as the most useful aspects. This was often perceived as the key element in helping to combat CFS. Although behavioural aspects of therapy were found to be useful, many young people struggled putting them in to practice. Tasks were often initially very hard to achieve, and parents found it challenging to watch their children push themselves. Some parents felt the agenda during the sessions was too narrow and rigid and therefore unresponsive to families' idiosyncratic issues.
	Inclusion of the family
	In addition to the sessions functioning as support for the parent, young people felt that they needed their parent/s at the sessions for emotional support or 'back-up' in this novel or daunting situation. Young people and parents both felt family involvement was important so that parents could understand the approach and could be involved practically by implementing advice and strategies and enforcing rules. It was also important that parents were present to absorb the advice since young people often reported extreme fatigue during sessions. Most young people reported being comfortable talking about issues in front of their parents. Many referred to the fact that parents were intensely involved in their illness and its management, so issues raised were not new or surprising to them. Despite this, many young people and a few parents felt that there were certain situations where the young person should have been seen alone and some issues that would be better discussed separately.

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Study	Dennison 2010[231]
	Psychological aspects
	Several young people disliked the 'psychological' or 'emotional' aspects, finding them irrelevant or inappropriate. Some young people and parents felt pigeonholed and subjected to generalisations. In particular, several young people felt they were being wrongly categorised as somebody with mental rather than physical health problems. The anxiety and depression questionnaire administered as part of the RCT contributed to this perception. Several young people and parents found the setting of the service within 'Psychological Medicine' inappropriate, in some cases upsetting the patient or inducing hostility. A small minority of participants from the psychoeducation group displayed frustration and fundamental disagreement with the approach and felt that the therapy overall was useless or even counterproductive. These participants had strong preferences for physiological explanations of CFS and deemed physiological approaches more useful and relevant. Others felt that the therapy was somehow incomplete and failed to tackle all aspects of the illness and psychological and emotional aspects appeared to be one area perceived to be ineffectively addressed.
	Effectiveness
	The therapy was useful to some extent, the family was thankful for the help, but improvements were modest and this was not a magic cure. However, participants particularly in the CBT group commonly reported that the therapy was a principle factor in allowing them to regain normality in their lives. The idea of therapy as a 'starting block' on a gradual journey to recovery was often mentioned. Participants described trying other treatments post-therapy and found these useful in different ways and for different aspects of the illness, but usually complementary to the therapy received. Other life changes such as personal growth, learning for maturity were deemed necessary for further improvement. Very few participants reported being 100% free from CFS. The majority experienced ongoing symptoms and limitations on activities and continued to see themselves as CFS patients with certain vulnerabilities. All of the young people's health had dramatically improved post-therapy and most participants found the extent of improvement acceptable. A minority, mostly parents, felt the therapy was insufficiently successful.
Limitations and applicability of evidence	No significant methodological limitations noted. Moderate concerns about applicability due to findings for both interventions being combined. PEM reanalysis: serious concerns about applicability due to existing reasons and it being unclear if participants had PEM (having been diagnosed using the Oxford 1991 or CDC Fukuda 1994 criteria where PEM was not a compulsory feature, as specified in the larger RCT for which participants were recruited)

Study	Harris 2017[313]
Aim	To explore what adolescents felt had caused their problems with eating, whether there were triggers and maintaining factors and what interventions they felt would be helpful.
Population	Adolescents with a primary diagnosis of ME/CFS, aged between 12-18 years who experienced at least one of the following: difficulty with eating, frequent nausea, lack of appetite, weight loss, abdominal pain, bloating, diarrhoea or constipation.

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Study	Harris 2017[313]
	The sample was drawn from a CFS/ME specialist hospital service providing regional support for assessment and treatment of over 300 children a year in the Gloucester, Bristol, Wiltshire and Somerset areas, covering a population of 400,000 children aged 5-19 years (Office of national statistics, 2011).
Setting	CFS/ME specialist hospital service
Study design	Qualitative interview study
Methods and analysis	Semi-structured interviews were conducted. Interview topics included the adolescents' experience of eating; the factors they felt caused and exacerbate eating difficulties and what they believed were helpful strategies. Interviews lasted approximately 30 minutes and were audio-recorded, transcribed verbatim and analysed thematically using techniques of constant comparison which commenced soon after data collection and informed further interview protocols. All adolescents were given the option to be interviewed alone or with a parent and seven chose to have their mothers present, all of whom contributed to the interview. Verbatim quotes from participants and mothers are used to illustrate themes.
Findings	**Seeking external support**
	Some adolescents took prescribed sickness or stomach acid relief medication which they found helpful. However, it was not common to have been offered medication to relieve their symptoms which frustrated some adolescents. Some families sought diverse treatments such as acupuncture, dietician input, sickness bands and the emotional freedom technique, while others spoke to their CFS/ME clinician for advice. External support varied greatly in perceived accessibility and helpfulness; therefore, outcomes across participants were inconsistent.
Limitations and applicability of evidence	Moderate limitations due to the role of the researcher; involvement of clinicians in determining participant eligibility that may have introduced selection bias and data richness. Moderate concerns over applicability due to the population being limited to adolescents with ME/CFS who experienced eating difficulties; findings may not be equally relevant to the wider population of ME/CFS who did not experience such difficulties. PEM reanalysis: serious concerns over applicability due to existing reasons and it being unclear if participants had PEM.

Study	Larun 2011[430]
Aim	To explore contexts of experiences of physical activity perceived as beneficial or harmful for CFS patients.
Intervention details	Six-week comprehensive treatment program for CFS patients including physical activities e.g. walking, hydrotherapy, relaxation and breathing exercises in addition to physiotherapy, theme discussions and individual counselling.

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Study	Larun 2011[430]
Population	Adults >18 years attending a treatment program for CFS. Participants joined the program for variety of reasons, not because they were particularly convinced of the benefits of physical activity. Purposive sample representing variations on gender, illness duration, and social background. N=10; male/female 2/8; mean age (range) 50 (40-64) years; mean illness duration (range) 3.4 (1-7.5) years; all scored close to maximum on the Chalder fatigue scale; none in employment.
Setting	Norwegian rehabilitation clinic.
Study design	Focus groups with thematic analysis.
Methods and analysis	Two focus groups took place at the clinic in a comfortable, quiet and dimly lit room. Focus groups lasted one hour, at a time of day when participants were rested. Authors acted as moderator and observer, using a topic guide and open-ended questions to encourage discussions between the participants. Participants encouraged to talk about their experiences of physical activity or exercise in a broad context, emphasising their perceptions of preconditions determining the subjective outcome. They were asked about their experience of physical activity after they became ill, whether the different experiences were perceived as beneficial or harmful and what characterised them as such. Physical activity beyond the clinic's specific program was explicitly requested. Focus groups were audiotaped and transcribed. Analysis using principles of systematic text condensation undertaken by two authors and interpretations and categories were negotiated until agreement was obtained. Tentative themes were identified, units of meaning relating to physical activity were identified and coded, coded data were condensed and abstracted within each category and the content of each group presenting differing context was synthesised and re-narrated.
Findings	**Flexible and individual adaptation is simpler with leisure activities**
	Participants reported an essential difference between leisure activities, which were perceived as enjoyable, and chores. Participants described experiences of becoming extremely ill after swimming, cycling, cross-country skiing, walking or doing strength exercises at fitness centres. Similar exercises undertaken outdoors in a non-organised way could be perceived as helpful and enjoyable and it was easier to adapt to the individual's energy level and hence did not make them ill.
	Several participants related that it was very easy to try to achieve too much too quickly but listening to the signals from the body could help them increase awareness and adequate responses and reconstitute quicker. Small and specific exercises done in a controlled manner were perceived as facilitating the process of getting to know their own body. Bed rest or decreasing total workload in advance could make it possible to prepare for exercises to be done later. Almost all participants related that relaxation exercises brought on better rest.
	'Push-crash' – losing control and feeling betrayed by their bodies
	Participants described different ways of experiencing lack of control over their bodies after exertion subsequent to non-customised activity. Some related how they would struggle to get home after exercises and a feeling that something completely wrong had

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Study	Larun 2011[430]
	happened to their body. Some described a paralysed feeling subsequent to activity, others experienced extreme exhaustion, muscular jerks or clumsiness, loss of balance, visual impairments and loss of concentration and ability to communicate. Several participants reported a decrease in physical ability and strength and a feeling of physical and mental paralysis if they were inactive over a period of time. During these setbacks, participants described experiences of dizziness and nausea when bending down and headaches, particularly when feeling tired or pressured.
	Review of energy usage in daily life towards better priority and balance
	Reviewing the daily workload with an occupational therapist was helpful for participants before they entered the rehabilitation program. Mapping exercises helped them to develop priorities of which tasks were important and which were not. Reviewing activities, putting expectations aside and letting things happen was reported to diminish stress. By keeping a diary of everyday life, participants recognised emerging patterns. Concrete and individually adapted advice was perceived to be helpful, especially when it took into account the balance between rest and exercise. Several participants would have liked a personal coach or assistant.
Limitations and applicability of evidence	Moderate methodological limitations due to recruitment strategy (self-selected participants and clinic staff helped to recruit participants), unclear relationship between researcher and participants. Moderate concerns about applicability due to setting (several references to farming suggests rural area) and aim of the study to elicit responses regarding physical activity beyond the clinic's specific program. PEM reanalysis: serious concerns over applicability due to existing reasons and it being unclear if participants had PEM.

Study	Picariello 2017[589]
Aim	To explore the experiences of patients with CFS who undertook CBT at a specialist service for CFS.
Intervention details	Face-to-face CBT from experienced therapists, guided by a standardised CBT manual and with regular clinical supervision. Sessions were typically fortnightly, with up to 15 sessions, depending on progress and agreement between the client and therapist. Participants were offered follow up sessions at 3, 6 and 12 months after the end of treatment.
Population	Patients who had finished CBT or were in the follow up stage, recruited consecutively. Participants were excluded if they did not have a diagnosis of CFS. N=13; male/female 2/11; age range 18-24 (n=1), 25-34 (n=7), 35-44 (n=2), 45-54 (n=2), 55-64 (n=1).
Setting	Recruited from a specialist outpatient unit, UK.
Study design	Semi-structured interviews with thematic analysis.

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Study	Picariello 2017[589]
Methods and analysis	Semi-structured interviews either face-to-face or by telephone. Interviews were digitally recorded and transcribed. Transcripts were analysed using inductive thematic analysis. This included extracting initial codes, incorporating emergent codes into broader themes and development of a coding manual. Grounded theory techniques were also used: constant comparison, generating a storyline and diagramming. Data coded separately by two authors, discrepancies discussed and themes modified accordingly.
Findings	**Hopes and expectations**
	As the process of treatment continued, participants' feelings of confusion and apprehension at the beginning of therapy were replaced by feeling as ease. The majority of participants reported high levels of satisfaction with treatment and in some cases felt that the treatment exceeded expectations.
	Validation
	Treatment was perceived as a source of validation. Participants stated that CBT helped them to feel understood and to reaffirm that their suffering is real and recognised. CBT provided a non-judgemental environment for participants to express themselves.
	CBT as support
	Participants were comforted by the knowledge that the therapist was available to them if they needed help. The simple act of talking to someone was of benefit to participants. To some, the support of CBT acted as a form of safeguard even when sessions were spread out over time. Many participants felt they would have liked the support of additional sessions; many feared a relapse and did not know how they would cope without CBT.
	Rapport
	Participants valued building a relationship with the therapist and reported a preference for face-to-face consultations. Some patients found face-to-face consultations to be more personal and enabled them to be more forthcoming.
	Personalised care
	Participants felt that the treatment was shaped by both the client and the therapist, feeling in control and being able to contribute and guide the content and structure of the sessions. Participants appreciated the fact that the therapy was adaptable to their needs.
	Motivation and engagement
	Participants recognised that in order to benefit from CBT, one must be ready to invest effort in it and motivation must come from within. However, the ability to invest effort might depend on illness severity and personal circumstances at the time of therapy. Some participants felt that starting CBT was more suitable at a time when symptoms were less severe. Participants found self-monitoring tasks useful, but at the same time found some tasks tedious or difficult to fit in to their routine.
	Gain and loss
	Improvement was closely linked to a mastery of the self-monitoring process and an awareness of behaviours or cognitions that may be contributing. Learning to plan and manage activity according to one's energy levels allowed participants to sustain improvements following CBT. Skills to manage and plan ahead and not to succumb when symptoms arise helped to counterbalance any

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Study	Picariello 2017[589]
	apprehension of relapse. Through CBT participants found it easier to be compassionate to themselves, avoiding 'boom and bust' patterns of behaviour. Some participants reported an unwanted consequence of a more consistent behavioural routine was discontinuation of loved hobbies and activities, although they were able to see the benefits.
	Usefulness of CBT specific components
	Participants reported finding behavioural tasks such as activity or sleep monitoring to be helpful in facilitating the development of self-awareness. Feedback on the cognitive aspects was mixed, with some participants perceiving it as crucial and others finding it less useful, especially for physical symptoms.
	Improvement/change
	Change was gradual and participants often reported not being aware of the improvement until they reflected on where they started. For some, the improvement was more apparent to those around them. Participants who felt they benefitted from CBT often reported improvements in wellbeing, although not to a pre-morbid level of functioning. A minority felt that their improvement was only slight and another felt they had not improved at all.
Limitations and applicability of evidence	Moderate methodological limitations due to recruitment strategy (only participants who had completed treatment), unclear relationship between researcher and participants. No concerns regarding applicability. PEM reanalysis: moderate concerns over applicability due to participants meeting criteria where PEM was not compulsory; by reviewing the study references, the reviewer interpreted the study to have included a sub-set of participants from a larger RCT (Burgess 2012) [111] based on the description of recruitment and treatment protocol. RCT (n=80) including participants meeting both the CDC (Fukuda 1994) and Oxford (Sharpe 1991) criteria.

Study	Pinxsterhuis 2015[592]
Aim	To elicit participants' experiences with a multidisciplinary patient education programme and their views regarding the usefulness of the programme immediately and nine months following participation in the programme.
Intervention details	Patient education programme developed, conducted and adjusted several times by health care workers in cooperation with two peer counsellors (CFS patients) prior to the study. Programme intended to promote coping by providing participants with information illuminating different aspects of the illness and included the following topics: coping skills, current medical approaches, personal relationships, pacing and energy conservation, physical exercise, relaxation, nutritional approaches and economic self-sufficiency. Programme lecturers were experienced health care workers (physician, occupational therapist, physiotherapist, psychiatric nurse, dietician and social worker) with competence in CFS. A peer counsellor shared their experiences and useful coping skills and acted as a positive role model. 8 x 2 hour sessions over 9 weeks including lectures and group discussions.

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Study	Pinxsterhuis 2015[592]
Population	Participants in the CFS patient education programme. Participants were excluded if their diagnosis did not comply with the Canadian diagnostic criteria (Carruthers 2003) and/or CDC 1994 criteria. N=10; male/female 2/8; mean age (range) 43.7 (32-57) years; illness duration mean (range) 6.6 (2.5-13.5) years; one participant was working.
Setting	Unclear; programme was delivered at a single hospital in Norway.
Study design	Focus group semi-structured interviews
Methods and analysis	Semi-structured interviews lasting 95-110 minutes and covering topics such as perceived helpfulness of the different sessions, perceived benefits of the whole programme, ideas regarding the illness, psychological coping processes and applied coping strategies. Interviews were audio-recorded and transcribed. The first author acted as the moderator and the second or third author was an observer. Thematic analysis, involving topic coding, comparison and relation of topics to each other and abstraction, applied as an ongoing flexible process. Analysis primarily conducted by one author, with involvement from a second author during the last step.
Findings	**Better understanding**
	Participants realised that they were actually ill and some expressed greater confidence regarding their diagnosis and awareness their symptoms were related to CFS. Some participants felt more able to assess information about the illness and treatments more critically. Learning about the diagnosis, symptoms, possible causes and prognosis increased understanding and confidence. It was considered helpful to learn that deterioration may occur even when doing everything 'right'.
	Acceptance
	Participants described a change in their understanding of the illness trajectory. Some participants had expected participation in the programme to cure them, but then realised that they had to focus on acceptance and coping with the illness. All participants experienced increased acceptance of the illness, although at times still felt that acceptance was equivalent to giving up hope of getting better.
	Coping
	Participants found it especially helpful to learn about pacing and energy conservation, relaxation exercises, how to deal with difficult feelings, economic and public support systems and nutrition. Immediately following the programme, participants felt they had gained new insights and understandings and envisioned new way of coping. Nine months later, they had begun to use new coping strategies in daily living, although to varying degrees. They experienced better coping with their illness and increased feeling of control but did not experience better health. Most participants believed they had gained a better insight into the relationship between activity level and symptom severity and felt better able to cope with symptom exacerbations. Resting more than they were accustomed to was experienced to prevent deterioration. Participants gained a better insight into the amount of energy required for different activities and felt more able to prioritise their use of energy, which occasionally included saying 'no'. Some participants had begun using assistive

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Study	Pinxsterhuis 2015[592]
	devices such as shower stools, work chairs and wheelchairs. Several participants had made changes to their diets, including spreading meals over the day, drinking more water and consuming foods with low carbohydrate content. Others felt unable to changes their diets because they lacked the appetite or energy. Some participants reported feeling more confident talking about the illness with others and had started using new strategies for dealing with people's misunderstandings and negative attitudes. Several participants wanted more guidance or follow-up to maintain the coping strategies after the programme.
	Exchange of experiences with fellow participants
	All participants found it helpful to exchange coping experiences and share beneficial coping strategies. For some, this was the most valuable part of the programme.
	Receiving understanding and acceptance
	It was an overall positive experience for participants to receive understanding and acceptance from fellow participants that were experiencing the same type of symptoms and problems. Mutual understanding made it safe to discuss issues they had not been able to discuss elsewhere. The presence of a peer counsellor increased the feeling of safety and fellowship and was valued as an important role model. Participants appreciated meeting health care professionals with knowledge of CFS.
Limitations and applicability of evidence	Minor methodological limitations due to data analysis (mainly by one researcher) and unclear relationship between researcher and participants. No concerns regarding applicability. PEM reanalysis: moderate concerns over applicability with PEM being a compulsory feature in only one set of criteria used to exclude participants (Canadian, Carruthers 2003) but not the other (CDC 1994).

Study	Reme 2013[621]
Aim	To explore the experiences of young people with CFS/ME after they had undergone the Lightning Process. Specifically, to increase understanding of beneficial and possible adverse effects of the Lightning Process, as well as the participants' attributions of the particular aspects of the programme that caused the effects.
Intervention details	Seminars (3-5 hours) run on three consecutive days. Participants learn about 'the physical emergency response', described as the body's natural response to threat and involves the activation of the sympathetic nervous system and production of hormones, which could have detrimental effects on different body systems if sustained. Participants are further introduced to the 'physiological catch 22', which is an important element of the process; this involves an onset 'event' which results in creating an extreme physical emergency response. The physical emergency response stimulates the sympathetic nervous system and the increased and prolonged response in combination with the original symptoms lead to a downward spiral, which is further worsened by emotional distress. By learning about these physical processes and how to influence them, participants are expected to recover from their CFS. Participants learn how to

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Study	Reme 2013[621]
	spot when the physical emergency response is occurring, how to calm it, and how to make this change permanent by practicing the steps until they become automatic. The process can be done in group sessions or one on one.
Population	Young people who were English speaking, aged 11-25 years and who had undergone the Lightning Process, recruited through an advertisement on the Association of Young People with ME website. Three young people were 18 years of age or under and thus supplementary interviews were conducted with their mothers. N=9; male/female 1/8; age (range) 14-26 years; illness duration (range) 2-12 years; 8/9 met Shape 1991 criteria for CFS prior to undergoing the Lightning Process, 7 of these no longer met the criteria at the time of the study.
Setting	Telephone-based interviews, UK
Study design	Semi-structured interviews
Methods and analysis	A single semi-structured interview (10-60 minutes, mean (SD) 21.4 (13.4)) approach explored the therapeutic experiences of patients and families. Following initial establishment of rapport, open-ended study questions were posed. Other questions and prompts were provided as necessary in response to issues spontaneously raised by participants. It was highlighted that researchers were interested in all experiences good or bad. Questions were pursued in a non-directive manner and participants could take breaks at any time, but none chose to do so. Interviews were audiotaped and transcribed. The interviewer was not associated with the Lightning Process programme or organisation and this was made clear to participants. Inductive thematic analysis, involving the detection of themes within the data, combining the analysis of frequency of codes with analysis of their meanings in context. Manifest themes were coded and the categories were refined by splitting, splicing and linking codes. Reliability of the codes was further tested by applying the same codes to the same text on two occasions, to ensure consistency in the distinction between the codes. Two case histories of contrasting examples were constructed from the data and used to shed light on where the therapy experience fitted into particular participants' experiences.
Findings	**Overall experience** **a) Positive** Most found the format acceptable and helpful. **b) Intensive** Several comments were raised regarding the intensity of treatment being too high. **c) Confusing** The information given in the first session was described as difficult to understand and challenging. The educational part of the intervention was considered as complicated and difficult to understand, but necessary and helpful. **d) Hard work** The majority of participants described the process as hard work, although one participant described finding it easy. **e) Conflicted with other treatments**

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Study	Reme 2013[621]
	The information given conflicted with that of other therapists. In particular, advice that participants could do anything they wanted conflicted with previous advice they had been given around activity pacing. **f) General impression of effectiveness** Some participants experienced an instant healing, some experienced a gradual improvement that continued after treatment ended and some did not find the treatment helpful. One participant's experience was dominated by a negative experience with one particular provider who was described to be too evangelical about the treatment and not sufficiently understanding and supportive.
	Treatment components that were helpful
	a) Learning the theory behind the Lightning Process Several participants highlighted that the educational part of the treatment, where they learned the theory behind the Lightning Process and which included practical examples of previous success stories, gave them a rationale they could believe in. Particular parts of the theory they found helpful were the association between thoughts, emotions and body, and how negative thoughts and emotions can affect the body directly. Some were unsure whether the theory was scientifically valid, but they still found it logical and believable. **b) Meeting others with CFS** The support from others and the group setting that allowed the participants to learn from each other was highlighted as helpful as aspects leading to engagement and treatment commitment. **c) Examples of treatment success** Several participants highlighted that the educational part of the treatment, which included practical examples of previous success stories, gave them a rationale they could believe in. **d) Positive and encouraging staff** Therapists and staff were mostly described as positive and encouraging. **e) The group setting** The support from others and the group setting that allowed the participants to learn from each other was highlighted as helpful as aspects leading to engagement and treatment commitment. **f) The practical assignments** The practical assignments were described as important for the rapid recovery. **g) Practicing the process and applications to everyday life** Participants had the opportunity to practice the process and apply it in their everyday life and they also realised that it was their own choice that would really help them recover. The behavioural aspects of the treatment stood out as the most important factor for symptom alleviation and continuing recovery. **h) The one-to-one sessions** **i) Setting of specific goals** The focus on specific goals and identifying barriers from reaching them was considered a helpful part of treatment.
	Treatment components that were unhelpful
	a) Sessions were too long

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Study	Reme 2013[621]
	The length of the sessions was thought to be too long and intense, especially since many participants struggled with focus and concentration. Others described the whole treatment as too short; with too little follow up afterwards. **b) Incomplete explanation of the physiology** Some found the teaching confusing and incomplete and not well-organised. **c) Not honest about the success rate** Participants mentioned the dishonesty staff showed when they claimed the treatment had a 100% success rate. **d) Inducing guilt if no recovery** Those who did not recover from the treatment felt that they were blamed for the lack of treatment success and consequently struggled with feeling of guilt and anger. **e) Pressure to be positive** Alternative viewpoints brought up by the young people were not well-received and a few experienced a normative pressure to be happy all the time and not express any negative feelings, which they found difficult. **f) Expecting too fast recovery** Participants criticised the impression that staff gave about the Lightning Process always involving a quick recovery. **g) The secrecy around it** The secrecy surrounding the Lightning Process was criticised and thought to result in unnecessary sceptical and prejudiced attitudes from people. Participants were specifically encouraged not to talk to anyone about it and they found this unhelpful and difficult. **h) Too dominant therapist** There were different opinions about the therapists; some had only good experiences, while others found their therapist too controlling and not open for critical questions. **i) The cost** The cost was mentioned as a negative aspect.
Limitations and applicability of evidence	Moderate methodological limitations due to recruitment strategy (single charity; more likely to be patients who did not recover) and data analysis (insufficient data presented to support all findings). No concerns regarding applicability. PEM reanalysis: moderate concerns about applicability due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on any additional criteria met.

Study	Taylor 2017[728]
Aim	To explore the experiences of young people with CFS/ME and depression in order to understand their views on why low mood developed, the impact of having low mood and what they had found to be helpful and unhelpful in treatment.

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Study	Taylor 2017[728]
Intervention details	Various interventions
Population	Young people aged between 12 and 18 years with a primary diagnosis of CFS/ME and co-morbid low mood (defined as a depression subscale score of >9 on the Hospital Anxiety and Depression Scale), recruited from a specialist paediatric CFS/ME service provided by a multidisciplinary team of doctors, occupational therapists, physiotherapists and psychologists. Those who were housebound (unable to attend outpatient appointments) were excluded. N=9; male/female 1/8; age median (IQR) 14 (14-15) years; illness duration median (IQR) 12 (8.5 to 37.5) months; 78% (7/9) had <40% school attendance, i.e. 2 days or fewer per week.
Setting	Participants' homes and by telephone, UK
Study design	Semi-structured interviews with thematic analysis.
Methods and analysis	A semi-structured topic guide was developed for the interviews, focusing on the young person's responses to the depression items on the HADS questionnaire, why young people felt they had become low in mood, factors contributing to low mood, whether their CFS/ME preceded or followed their low mood, what treatment strategies were helpful and unhelpful and whether anything else would have helped. Six young people were interviewed alone, and three with a parent present. Interviews were digitally recorded and transcribed. Three researchers each independently read through the first three transcripts and generated potential codes. Researchers then met together to discuss and compare codes, and began to combine the codes into themes. This process continued iteratively through the remainder of the analysis. NVivo was used to analyse the data thematically using techniques of constant comparison. Thematic analysis was used as a means of identifying, analysing and reporting patterns in the data.
Findings	**Individualised approach**
	Young people found different approaches helpful. The importance of an individualised approach was emphasised.
	CBT
	Some participants talked about finding CBT helpful. The combination treatment of CBT and medication was also discussed. One participant talked specifically about how they continue to use CBT in their lives, demonstrating a clear understanding of the cognitive behaviour therapy model and principles.
	Activity management
	Young people recognised that AM could be a helpful approach, for example, by giving them things to look forward to. Achieving a balance of activities within one's limits was emphasised. At times, participants also talked about having to think more about what activities they invested energy in, which in itself seemed to detract from the experience of the activity itself to some extent, thus undermining their sense of enjoyment and/or achievement in the activity.
	Medication

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Study	Taylor 2017[728]
	Young people generally did not mind taking medication providing they found it helpful.
	Other helpful strategies
	Young people felt that better support from education systems could have helped. Participants also felt that building supportive networks could be beneficial; this includes developing relationships with other young people with CFS/ME. They talked about the potential being of feeling understood and less alone.
Limitations and applicability of evidence	Minor methodological limitations due to data analysis (insufficient data presented to support all findings) and no clear statement of all findings. Moderate concerns about applicability due to study population (ME/CFS with comorbid depression). PEM reanalysis: serious concerns about applicability due to existing reasons and it being unclear if participants had PEM.

Study	Ward 2008[826]
Aim	To explore users' views and perceptions of their experiences of counselling, in particular what they found useful and what they found unhelpful or negative.
Intervention details	Any type of counselling intervention delivered by a counsellor, therapist, or clinical psychologist. Length of counselling ranged from eight weeks to one year and included both NHS and private settings. From the material, authors concluded that participants had experienced CBT, person-centred, psychodynamic and integrative/eclectic approaches to counselling.
Population	People who had received a formal diagnosis of ME from a medical practitioner and who had experienced any type of counselling intervention recruited through advertisements in the newsletters of the ME Association and the Action for ME user group. N=25; male/female 4/21; age mean (SD, range) 44 (11, 23-65) years; illness duration (range) 2-19 years.
Setting	Telephone based interviews, UK
Study design	Unstructured interviews
Methods and analysis	The interview began with a general introduction and the direction was determined by the interviewee, with the interviewer prompting and encouraging. Participants were offered to be interviewed over a number of sessions if this was helpful, but this was not necessary for any participants. Interviews lasted 20-90 minutes, were digitally recorded and transcribed. Interview transcripts were analysed using thematic analysis by the authors following grounded theory principles and the resulting thematic structures were compared and discussed until the final thematic structure was derived.
Findings	**Experiences of different types of interventions**

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Study	Ward 2008[826]
	a) Activity related interventions Activity management included devising routines, increasing the level of activities, keeping diaries, setting goals and pacing. Of these the most useful was pacing – this was the most valued aspect of all counselling interventions. Participants described how in the early stages they often got this wrong, resulting in periods of crushing fatigue and pain. Exploring the relationship between activity and energy level was complicated by the fact that there was often a delay of sometimes several days before the full impact was felt. For these participants, exercise regimes and sometimes activity programmes were viewed negatively. Participants were often pushed to overdo it, leading to significant relapse.
	b) Stress-management interventions Relaxation and meditation techniques were viewed positively, with participants talking of reduced stress levels in terms of the impact of their condition and their life activities.
	c) Thought management interventions Responses to thought management strategies were mixed, with some participants finding suggestions of negative thoughts being counterproductive to be patronising and negative. Some felt that their condition was being blamed on their negative outlook. Some participants found such notions simplistic. Other participants found such interventions very useful, for example in helping them to counter very unrealistic or catastrophizing reactions.
	d) Examining the influence of the past interventions Very few participants experienced this approach. Those who had felt very negatively about it because they thought the suggestion was that the cause of their ME might be rooted in the past and they firmly rejected any psychological cause for their condition.
	Reflections on the nature of the relationship with the counsellor
	a) Negative reflections Negative reactions to counsellors involved poor communication, counsellors not understanding the condition and non-empathic responding.
	b) Positive reflections Positive reflections involved counsellor listening, understanding and offering appropriate challenge.
	Reactions to counselling
	a) Negative reactions Several participants mentioned the physical impact of the counselling on someone with severe ME. They described the difficulty of making their way to and from the session each week and the strain of keeping up a session of 50 minutes. The majority of the negative reactions related to perceptions of the counsellor and the counselling process. The suggestion that their condition might not be physical, that they have control over it, or that its roots lie in the past could be found to be very challenging and certain types of counselling were perceived as controlling, patronising and a form of brainwashing. These perceptions generally related to what participants understood as CBT.
	b) Positive reactions

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Study	Ward 2008[826]
	Positive reactions involved feeling listened to by an empathic counsellor who understood the condition.
	Perceived benefits of counselling Perceived benefits of counselling were a good relationship with someone who understands and who is outside of the immediate situation, having a weekly stimulus, coping with stress, having realistic goals and learning to pace.
Limitations and applicability of evidence	Moderate methodological limitations due to recruitment strategy (ME charities; more likely to be patients who did not recover), research design (unclear interventions, based on participant recall) and data analysis (insufficient data presented to support all findings). Minor concerns regarding applicability due to unclear interventions. PEM reanalysis: serious concerns regarding applicability due to existing reasons and it being unclear if participants had PEM.

Call for evidence

Study	Snounou 2019[690]
Aim	To evaluate, through focus groups and feedback questionnaires, the experience of patients who participated in an eight-week group condition management programme for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (ME/CFS)
Intervention details	Two-hour session weekly over eight-weeks, led by an occupational therapist and overseen by a dietician and a physiotherapist. Each session included a presentation followed by group discussion and each session was based around a different topic. The Programme aims to take a holistic approach to support patients living with ME/CFS, to stabilise activity levels and to work towards a gradual increase whilst monitoring the body's response. The topics covered within the Programme included: understanding ME/CFS, coping with emotions, rest, activity and sleep, stress management, diet, physical activity, and communicating with others. The programme was based on a group programme named the Step Programme carried out at Yorkshire Fatigue Clinic and adapted to the needs of the population, including consultation with a patient living with ME/CFS.
Population	People who had taken part in the eight-week programme. To be eligible for the group programme, patients must have an established diagnosis of ME/CFS and be 18 years or older. The programme was only available to those with mild to moderate symptom severity. One participant had been unable to attend the group programme but received one-on-one sessions on the group content following the programme. N=16; male/female 3/13; age range 25-70 years; illness duration 4 participants with a diagnosis for 6 months - 1 year, 5 participants with a diagnosis for 1-5 years, 7 participants with a diagnosis for 5 years or more; 2 participants were working part time.
Setting	Meeting rooms in centres within the region that the study was carried out in, Northern Ireland

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Study	Snounou 2019[690]
Study design	Mixed methods, focus group interviews and feedback questionnaires.
Methods and analysis	Two focus groups including 8 participants each, facilitated by an occupational therapist using a pre-designed list of questions about experience of the programme. Notes were taken by a former occupational therapist and a patient with ME/CFS volunteering with the programme. No direct quotes were recorded from the focus groups. All patients present during the eighth weekly session of the first two group cohorts were asked to complete a feedback questionnaire on how the patients found the group programme, what they had learnt, and their view on the practicalities of the programme. Questionnaire responses were analysed, themes identified, and representative quotes for each theme extracted. Notes from the focus groups, in combination with the representative quotes from the questionnaires, were analysed, using a thematic analysis by constant comparison analysis (open coding, axial coding, and then selective coding), i.e. chunking the data into small units, grouping the codes into categories, and then developing a theme to express the content of each group. Additionally, some techniques from classical content analysis were used, through quantifying the number of pieces of data to which a particular code was given.
Findings	**Accessibility** **a) Time of day** Timing of programme being between 14:00-16:00 was good and they elaborated saying 'the timing of the group worked well, not too early'. **b) Venue accessibility** Having high backed supportive chairs throughout the programme was helpful. The lift was useful for times the room the programme took place in was not on the ground floor. **c) Lack of attendance pressure** There had been no pressure placed on attendees when they missed a week: they felt welcome at the programme and they appreciated how encouraged they felt to return to the programme. Anxiety about the implications of missed attendance came up again in suggestions for improvements with the suggestion to cover initial anxieties at the beginning of the first session e.g. 'What if I am too ill to attend a week?' **d) Handouts** Having handouts was good, especially if they were given out at the beginning of the session as it saved energy used if one had to take notes. One patient suggested having handouts available online would be useful. **e) Video Conferencing** It was suggested that incorporating video calls for example through Skype, Facetime or webcam would be useful for patients who were housebound at the time of the programme (including patients who are housebound long-term and those who may find themselves housebound during a particular week of the course.)

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Study	Snounou 2019[690]
	f) Duration of Each session There were mixed opinions on the duration of each session: One patient commented that the 'length of sessions was just right'. However, a couple of others felt that the sessions were too long and that 1.5 hours would be a more manageable duration than 2 hours.
	Programme content
	a) Overall The most appreciated topics on the course were pacing and activity management, rest and relaxation. These were followed by understanding the science behind ME/CFS, diet and relationships.
	b) Pacing and Activity Management It was beneficial to learn about the use of diaries, boom and bust patterns, knowing one's limits, prioritising, planning ahead, time management and pacing.
	c) Rest and Relaxation It was positive to learn how to rest properly, with one patient explaining they learnt to appreciate 'the importance of complete rest rather than reading or TV rest.'
	d) Science and Understanding ME/CFS No extractable findings; individual quotes only (quotes were positive).
	e) Diet Two patients expressed that the information regarding diet was beneficial.
	f) Relationships and ME/CFS Two patients emphasised the value of discussing the impact of ME on relationships within the programme. They felt it was positive to open up about impact on relationships with others, with people who understand i.e. the other patients doing the programme.
	g) Exercise/ Physical Activity One patient valued 'Emphasising the importance of regular [physical activity], and the opportunity to successfully complete [physical activity] without increase in symptoms.' However, another patient was unsure about the physical activity advice.
	h) Other topics Other topics included that the focus group thought to be important were learning 'not to be so hard on yourself' and the practicalities and the help available to return to work. Additional topics patients mentioned they would like to be covered included information on benefits, the impact of sunny weather (including heat and vitamin D), pain management and further information on stress recognition and management.
	Structure of the programme
	a) Positive aspects

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Study	Snounou 2019[690]
	Overall participants rated the structure of the programme as 'very good.' Participants felt the group size was appropriate. They felt that the GP referral to the programme had been fast and effective. Patients appreciated having the follow-up at three and six months. One patient commented on the venue of their group: 'The course being held in a leisure centre was good psychologically, separating it from a health setting.'
	b) Suggested changes Several people said they would like to be able to have one-off crisis-type access e.g. for during a deterioration or relapse and that some patients would require longer-term support. One participant commented that it would be helpful to 'Focus on one tool at a time to allow for implementation.' One participant expressed they would value 'time to create an action plan at the end of the session so you have a clear plan'.
	Group nature of the programme Participants placed great value on meeting other patients with the same/similar condition(s). They explained the group aspect of the programme helped create a support network for them. The patients that had one-on-one sessions in addition to the group sessions also deemed this as helpful.
	Perceived impact of the programme Not extractable findings; individual quotes only (quotes were positive).
Limitations and applicability of evidence	Severe methodological limitations due to recruitment strategy (only those who completed the programme were recruited), unclear relationship between the interviewer and the participants (interviewer was an occupational therapist; programme also led by an occupational therapist); data analysis (analysis by individual researchers; insufficient data presented to support all findings) and no clear statement of some findings. No concerns regarding applicability. PEM reanalysis: moderate concerns regarding applicability due to it being unclear if participants had PEM.

Study	Brigden[88] (Beasant[64])
Aim	To ascertain the feasibility and acceptability of conducting an RCT to investigate the effectiveness and cost effectiveness of GET compared to activity management for paediatric CFS/ME.
Intervention details	In both arms, clinicians could provide routine advice about sleep, medication use and symptom control. Families and clinicians decided upon the number of follow-up sessions (typically between 8 and 12) and the frequency of appointments (typically every 2-6 weeks). The interventions were delivered in secondary care outpatient clinics, delivered face-face in the hospital setting or via Skype. GET was delivered by a trained CFS/ME specialist (physiotherapists, occupational therapists, nurses or psychologists) in the outpatient setting. Advice was focussed on exercise (physical activity) with detailed assessment of physical activity at the start of treatment, and

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Study	Brigden[88] (Beasant[64])
	advice about finding a stable level (baseline). Therapists calculated the young person's "maximum" heart rate (220 minus their age). At the start of treatment, young people were advised to try and ensure physical activity levels were low enough so heart rate did not increase to more than 40-50% of this maximum heart rate. Participants were taught to monitor their heart rates (either manually or with a wearable such as a FITBIT). They were encouraged to use paper diaries/apps to monitor and record physical activity. Once the baseline level of activity was achieved and maintained, the young person was supported to gradually increase physical activity (10-20% a week). Therapists completed fidelity checks in each appointment to record the advice given. Advice on different types of cognitive activity, discussion about the different types of cognitive activities or Instructions to record the cognitive activities was prohibited in this treatment arm. Activity management was delivered by specialist CFS/ME clinicians (occupational therapists, physiotherapists, nurses and psychologists). The clinician assessed the participant's current levels of activity, including cognitive activities, emotional activities and physical activities. The clinician and participant then agreed a "baseline" of activity; a daily sustainable level of activity, typically the average daily amount of activity that the young person reported at assessment. Young people were taught how to record the total number of minutes spent each day doing different levels of activity (high-energy and low energy) using either paper diaries or the "Active ME" digital App. When participants achieved a "baseline" of all activity (cognitive/physical/emotional) they were supported to gradually increase activity by 10-20% each week.
Population	Children and young people (age 8-17 years) with a diagnosis of mild to moderate CFS/ME participating in an RCT (MAGENTA) and their parents. Participants recruited from three Specialist Paediatric CFS/ME services. Those who were severely affected (unable to do activity for themselves, only able to carry out minimal daily tasks, or had severe cognitive difficulties and depend on wheelchair for mobility), referred to CBT at their first assessment or unable to attend clinic sessions were excluded. Maximum variation sampling used to ensure a variation in characteristics and recruitment from both intervention groups. N=27 families from one centre (n=12 randomised to GET; male/female 5/7; mean age (range) 14.7 (10-17) years)
Setting	Participants' homes, in the hospital, via skype or by telephone, UK
Study design	Semi-structured interviews
Methods and analysis	Semi-structured interviews conducted with participants and parents who had consented to the trial. Participants were offered a choice of interview location: at home, in the hospital, via skype or by telephone. A checklist of topics was used to guide discussion, but participants were encouraged to raise issues they felt to be relevant and important. Interviews lasted between 15-60 minutes and were audio-recorded and transcribed. Five interviews were joint interviews with the parent and young person, five were primarily with the young person but with the parent resents and two were with the young person by themselves. Techniques of constant comparison were drawn upon to inform further sampling and ongoing data collection. Interview transcripts were coded using NVivo and analysed thematically. Common and divergent themes and individuals exhibiting contrasting views (negative cases) were studied in detail to understand reasons underlying such differences. Initial data analyses were initially undertaken by the

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Study	Brigden[88] (Beasant[64])
	qualitative researcher. To check coding reliability, other members of the team independently analysed a proportion of transcripts and compared findings.
Findings	**Core aspects of the specialist CFS/ME care package** Participants and parents in both arms commented on finding core aspects of the specialist CFS/ME care package beneficial, (such as sleep hygiene, referral to a psychologist and information about diet).
	Activity management Participants found the approach positive and helpful on the whole when managing CFS/ME symptoms. They highlighted that "limiting" high level 'red' activity could be challenging and frustrating, particularly in the run up to school exams. Recording cognitive activity levels on activity management sheets or the "ActiveME" App was seen as onerous for some, although parents and participants noted that overall activity management had a beneficial effect on their CFS/ME.
	GET - Exercises are enjoyable Despite mixed preconceptions, most participants were positive about GET once they entered treatment and reported positive experience of the exercises.
	GET - Importance of routine and structure Many families explained that the program introduced routine, which they experienced as important. Participants also described benefits of a more consistent routine from GET, including a regular waking/getting up pattern.
	GET - Relationship with clinician Many families valued the support they received from their clinician. Some comments recognised the helpful support of the clinician in dealing with the young person's school. Many families acknowledged the importance of the relationship in terms of having someone listen and understand and feeling cared for.
	GET - Individual tailoring Families consistently praised the way the program was implemented in a tailored way in which the clinician identified the individual needs of the young person and collaboratively developed a tailored treatment plan. Families commented that the GET program was tailored around the child's interests and activities and taking into account individual needs. Many commented on the program being adapted to the child's capabilities. Families felt that therapists delivering treatment recognised the fluctuating nature of CFS/ME and that physical capabilities change, including setbacks and "crashes", and that the program included flexibility with recommendations. Families also reported that they gained extra advice beyond the central focus on activity, such as sleep or diet, when these came up for participants.
	GET - Activity reduction and pacing **a) Activity reduction and pacing benefits** Some families commented that the treatment set helpful boundaries to avoid a pattern of overexertion. Many families explained that the clinician worked closely with them to make sure that activity and any increases were done at a manageable pace for the child. Some reported that clinicians were flexible in reducing the activity if the increase had been too rapid/ too much.

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Study	Brigden[88] (Beasant[64])
	b) Activity reduction and pacing challenges Some families reported that limiting activity was challenging, with evidence that the young person resisted this advice, wanting to do more physical exercise. Concerns about activity reduction included social effects and difficulties with limiting walking in school.
	GET - Setbacks during treatment A number of families described that the young person had a setback or "crash" during the course of treatment. Families reported that crashes or setbacks happened as a result of the young person exceeding their recommended limits of physical activity. Young people reported dealing with setbacks by adapting their activity levels to a lower level, supported by their clinician. There were reports that travel to the hospital site for appointments contributed to setbacks, which worsened fatigue in some young people.
	GET - FITBITS and physical monitoring Participants commented positively on the use of wearables to accurately detect physical activity, as this demonstrated when they were doing too much, making the participant aware of over-exercising. Participants enjoyed using the Fitbit, often finding other functionality such as sleep or steps monitoring useful in addition to heart rate monitoring. Some issues with Fitbits were identified including inconsistent availability: one was the wrong size, two participants reported not receiving Fitbits, one participant purchased one independently. Some comments indicated that the measurements were not always accurate, for example under-reporting numbers of stair climbs in a day.
	GET - Positive outcomes from treatment There were many positive reports of treatment outcomes from families, with overall recognition that the young person had benefitted from GET. Families commented on improvements to the young person's CFS/ME symptoms, including reductions in fatigue and tiredness, improved sleep and ability to concentrate. Several comments indicated improvements to the young person's functioning attributed to GET. Several families reported that treatment led to mood improvements in the young person.
	GET - Uncertain/lack of difference from treatment Some families did not notice a difference with treatment, either reporting uncertainty, or lack of impact, often related to school and cognitive activities.
Limitations and applicability of evidence	Very minor methodological limitations due to unclear relationship between the interviewer and the participants. No concerns regarding applicability.

Study	Anderson[22]
Aim	To assess the feasibility of recruiting families to a trial of a UK-adapted version of the Dutch CBT program: Fatigue In Teenagers on the interNET in the NHS (FITNET-NHS), compared to a version of usual care – Activity Management (delivered via Skype), and to assess the acceptability of the two interventions.

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Study	Anderson[22]
Intervention details	FITNET-NHS is an online modular CFS/ME-specific CBT program designed to be used by young people and their parents. It is supported by individualised clinical psychologist e-consultations (with messages sent separately to the young person and to the parent). There are up to 19 chapters for young people to work through, which are unlocked by the psychologist on completion of the previous one. Some chapters are optional and are only unlocked if the psychologist thinks they are relevant for the young person (e.g. a chapter looking more closely at mood problems). The earlier chapters include explanations of the links between thoughts, feelings and behaviour that form patterns that contribute to the maintenance of CFS/ME symptoms. The chapters include questions for young people to complete designed to identify unhelpful patterns and help with problem solving. Young people are encouraged to monitor their activity, establish a manageable baseline and build on this gradually. There are diaries included in the program, for young people to record their sleep, activity levels and helpful thoughts, which they can then discuss with therapists. Parents can read the content of chapters but not the answers to questions. Therapists are able to see question responses and diaries, and also use the tailored e consultations to help the young person through the course. Activity Management (AM) (via Skype) is the comparison treatment, delivered by a CFS/ME clinician (usually physiotherapist/ occupational therapist). AM is a standard behavioural treatment offered within the specialist service, and recommended by the National Institute for Health and Clinical Excellence (NICE). It involves assessment of the young person's activity level and begins with establishing a manageable baseline of activity to be maintained daily (usually reduction of activity) from which to build gradually and safely at a pace that the patient can manage. The AM intervention offered within the trial is protocolised, and explicitly prohibits detailed engagement with cognitions, keeping it as a behavioural treatment. AM was included as a version of usual care for comparison with the FITNET-NHS intervention treatment.
Population	Young people aged 11-17 with a diagnosis of CFS/ME (with no access to local specialist paediatric CFS/ME treatment) together with their parents/carers, recruited to a pilot trial (FITNET). Participants were purposively selected for maximum variation (intervention, age and gender). N=20 families (12 families in the FITNET-NHS-NHS arm and 8 in the Activity Management arm). This included 18 children, (male/female 6/12; age range 12-17 years) and 22 parents (19 mothers, 3 fathers, 2 interviews included both parents).
Setting	Skype/telephone-based interviews, UK
Study design	Semi structured interviews with thematic analysis
Methods and analysis	In-depth interviews with participants and their parents to understand their experiences and views of trial processes: provision and acceptability of patient information, reasons for accepting or declining participation, treatments preferences and acceptability of treatments. Particular focus on the use of the FITNET-NHS-NHS platform and Skype calls for Activity Management. Families were given a choice of being interviewed over skype or telephone, together or alone. Interviews followed a checklist of topics but allowed new issues of importance to emerge. All interviews were audio recorded with consent using encryption software, transcribed verbatim and anonymised. Qualitative data analysis was ongoing and iterative commencing soon after data collection to inform further data collection. Transcripts were imported into NVivo, systematically assigned codes and analysed thematically using techniques of constant comparison. Data

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Study	Anderson[22]
	were examined for patterns and themes, comparing accounts between different participants and refining the coding framework as interviews progressed. To check coding reliability, a proportion of transcripts were double coded and findings compared to check coding and interpretation by other members of the team.
Findings	**Acceptability of interventions** Feedback supported the acceptability overall of both intervention arms. Participants valued the individual tailored advice from a 'specialist' CFS/ME therapist as they hadn't had the support before.
	Acceptability of FITNET-NHS platform/ e-consultations with therapist Participants liked that they could complete the platform in their own time rather than having to attend appointments. Emails gave them time to think about their answers and some participants found it easier to talk about personal topics over email. However, others found it difficult to portray things in writing and would have preferred some face to face contact.
Limitations and applicability of evidence	Very minor methodological limitations due to unclear relationship between the interviewers and participants. No concerns regarding applicability. PEM reanalysis: moderate concerns over applicability due to participants in the original pilot trial (FITNET) for which they had been recruited meeting criteria where PEM was not a compulsory feature for diagnosis (CDC Fukuda 1994 criteria as specified in the quantitative evidence).

Study	Forward-ME survey 2019[564]
Aim	To describe the experiences of adults and children with ME/CFS who have participated in CBT and GET interventions. Describe the experiences within subgroups of modifiable and non-modifiable variables.
Intervention details	N=670 started a course of CBT; number of sessions ranged from 1 to 180 (most common 6); most commonly delivered by a cognitive behavioural therapist; most commonly individual treatment. N=428 started a course of GET; number of sessions ranged from 1 to 2100 (most common 6); most commonly delivered by a physiotherapist; most commonly individual treatment. N=725 started a course of CBT combined with GET; number of sessions ranged from 1 to 200 (most common 6); most commonly delivered by a cognitive behavioural therapist; most commonly individual treatment. N=707 started a course of GET combined with CBT; number of sessions ranged from 1 to 365 (most common 6); most commonly delivered by a physiotherapist; most commonly individual treatment.
Population	Inclusion criteria for participation in the survey was:

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Study	Forward-ME survey 2019[564]
	1. To have been offered or received CBT and/or GET since 2007 – even if the course was not completed AND 2. To have a diagnosis of ME, ME/CFS, CFS or PVFS confirmed by a clinician AND 3. To have received treatment within the UK N=2274; male/female 384/1829; age range 12 years and under (n=17) to 71+ years (n=25); 87% responses were self-reported, 8.1% of responses were completed on behalf of a child and 4% were completed by a carer on behalf of an individual with ME; 62.4% rated their condition as moderate before treatment; 98.5% experienced post exertional malaise.
Setting	Online survey, UK
Study design	Survey including closed ended and open-ended questions.
Methods and analysis	The survey data was exported from the Qualtrics platform (Qualtrics, Provo, UT) and converted to a SPSS (IBM, SPSS Statistics, Version 25) data file. The open-ended questions were analysed through NVivo 12 Plus qualitative data analysis Software (QSR International Pty Ltd. Version 12). The software automatically coded themes by sentence, indexed words using a word frequency count and coded responses into sentiment, highlighting negative or positive responses. Each open-ended question has been reported primarily by theme and word frequency. Sentiment categorisation has been applied mainly to the survey end questions.
Findings	**Reasons for stopping CBT** Respondents mentioned they were too ill to continue, including worsening of symptoms of post exertional malaise (PEM), stress and anxiety. In addition, many respondents quoted treatment being stopped by the practitioner due to detrimental effects or CBT being unnecessary for the individual.
	Worsening of symptoms (CBT) Common themes in responses included fatigue, cognitive issues, pain, and activity levels.
	Reasons for stopping GET Respondents mentioned an increase of symptoms, pain, discomfort, deterioration and relapse for stopping GET.
	Worsening of symptoms (GET) Top coded themes included pain, fatigue, muscular symptoms, cognitive issues, malaise, brain fog, and mental well-being.
	New symptoms (GET) The top coded themes included pain, sensitivity, muscular symptoms, joints, and brain. In addition, the word frequency count highlighted ideas related to disease/symptom severity and ability to walk.
	Reasons for stopping combined CBT and GET – responses related to CBT Respondents mentioned they were too ill to continue with worsening of symptoms, inability to keep up with attendance, and being discharged from the service.
	Worsening of symptoms (responses related to CBT) Top coded themes included brain, mental, pain, health, symptoms, cognitive, function, energy and malaise.

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Study	Forward-ME survey 2019[564]
	Reasons for stopping combined CBT and GET – responses related to GET Top themes included exercise, activity, symptoms, pain, malaise, session, health, worsening, and illness. Many respondents mentioned an increase of symptoms, pain, deterioration and worsening as reasons they stopped GET.
	Worsening of symptoms (responses related to GET) Top coded themes included pain, muscle, brain fog, health, mental health, levels, symptoms, cognitive, malaise and fatigue.
	New symptoms (responses related to GET) The top coded themes included pain, problems, muscle, joint, symptoms, issues and cognitive.
Limitations and applicability of evidence	Moderate methodological limitations due to recruitment strategy (ME charities; may be more likely to have not improved/recovered; unclear detail on interventions received); data collection (open ended questions focussed on negative aspects of treatment – reasons for stopping and how symptoms worsened); data analysis (individual quotes and data analysis software coded themes by sentence, indexed words using a word frequency count and coded responses into sentiment). No concerns regarding applicability. PEM reanalysis: moderate concerns regarding applicability as the experience of PEM was self-reported and diagnosis was confirmed by a clinician, but it was not specified if or which diagnostic criteria were used.

Study	ME Action 2019[435]
Aim	To supply NICE with up to date patient data.
Intervention details	68 ME services. The top 10 clinics attended by 28 or more respondents were: • Bristol CFS/ME Service for Adults • Sheffield CFS/ME Service for South Yorkshire and North Derbyshire • Norfolk and Suffolk ME/CFS Service • Liverpool CFS/ME Management Services • Leeds and West Yorkshire CFS/ME Service • Bath Specialist Paediatric CFS/ME Treatment Service • Surrey - South West London and Surrey Chronic Fatigue Service • Oxfordshire CFS/ME Service • Essex Chronic Fatigue Service ● Edinburgh - Lothian CFS/ME Service

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Study	ME Action 2019[435]
Population	N=1,886 who completed valid questionnaires and had a diagnosis of CFS/ME, ME/CFS, ME or CFS; 99.3% responded that they experienced post-exertional malaise
Setting	Online survey, UK.
Study design	Survey including closed and open-ended questions with thematic analysis.
Methods and analysis	Questionnaire distributed via social media and email to charity contact list. Responses were anonymous and respondents were allowed to fill in the survey more than once if they had attended more than one ME service. Open-ended comments have been analysed using thematic codes based on the main areas of comment and summaries of this analysis are reported.
	Clinic offers graded exercise therapy/condition worsened due to GET. The impact of being told to do graded exercise therapy and the harm caused to respondents by following this advice was a key issue, particularly for those who wanted clinics closed or adapted.
	Given bad/poor information/advice/treatment. There was a range of comments about inappropriate advice, with many highlighting information relating to treating ME as a psychological disease or based on the GET or CBT models of treatment (or both). Comments also highlighted that supportive staff were often handing out information that was outdated or inappropriate.
	Clinic offers CBT based on belief it will help with symptoms of ME. Criticisms of CBT related mainly to the therapy being used as a 'treatment' for ME rather than it having a negative impact on health.
	Pacing as effective approach/ clinics not able to support pacing effectively. Most comments on pacing were positive, although some respondents with a positive experience of pacing felt that the clinic should offer more advice. Not all those that had been advised on pacing felt that the advice was helpful.
	Advice/Interventions in those who had not attended a clinic Key themes were exercise (graded exercise therapy GET, increasing activity levels), being a negative experience/experience deterioration or a desire that they had not followed this advice from healthcare professionals; pacing or managing activity and rest either as something they found useful or something that they wish they had been told earlier/could receive; CBT/psychology as a negative experience or mention of CBT/psychology, not finding this intervention useful; rest- either that they found it helpful, or wish they had been told to rest earlier; and antidepressants- being prescribed for ME symptoms by health care professionals, and the experiencing of negative side effects.
Limitations and applicability of evidence	Serious methodological limitations due to recruitment strategy (single ME charity; may be more likely to have not improved/recovered and the diagnosis being self-reported); research design (unclear detail on specific interventions received); data analysis (limited detail reported on methods of data analysis); no clear statement for all findings (some findings are vague, mentioning 'positive' or 'negative' comments). Moderate concerns regarding applicability due to lack of information on participant characteristics including PEM which was self-reported.

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Study	Bristol CFS/ME Service[90]
Aim	Not explicitly stated.
Intervention details	The Bristol Chronic Fatigue Syndrome/ME Service. If a diagnosis of CFS/ME is confirmed at assessment, patients are invited to attend a pair of seminars held every month. The aim of the seminars is to introduce newly diagnosed CFS/ME patients to key areas of knowledge about the condition, and to introduce a foundation for self-management and rehabilitation. Each month the group consists of approximately 15-25 patients, who are invited to contribute their experiences of CFS/ME during the seminar, so that the seminar is co-created by clinicians and patients. An additional contribution may be made by a previous patient of the Service who has made progress by applying the approaches that the Service encourages. The first seminar aims to provide a foundation of basic knowledge about CFS/ME, and draws on patient experiences in order to explore topics such as: • the core symptoms and the other, less frequent symptoms • common triggers • the model of CFS/ME used within the Service • the biological, psychological and social consequences of living with CFS/ME • managing post-exertional symptoms (the 'boom and bust' cycle) The second seminar focuses on more advanced knowledge and coping strategies related to: • the use of diaries for activity analysis • the role of recuperative rest • sleep management • stress management After patients have attended both of these sessions, a follow-up appointment is arranged, normally with the therapist who assessed the patient. At this appointment, a further management plan is agreed. Shared decision making is an important aspect of these review appointments.
Population	People with newly diagnosed CFS/ME attending CFS/ME seminars Number of participants and characteristics not reported.
Setting	Bristol Chronic Fatigue Syndrome/ME Service, UK
Study design	Qualitative service evaluation form and thematic analysis.
Methods and analysis	Patients were invited to fill out a qualitative service evaluation form which asked about the most useful and also the most difficult aspects of attending the two seminars. A thematic analysis was conducted by three team members who discussed the responses until a consensus was reached.
Findings	**Benefits of attending the foundation phase seminars**
	a) Information

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Study	Bristol CFS/ME Service[90]
	A common theme was how informative the sessions were for the patients. Many attendees commented that the sessions expanded their knowledge of CFS/ME and offered different ways of managing their symptoms. Whilst for some, the seminars reinforced knowledge that they had already gathered, for others the seminars offered more understanding about the condition and helped with “sorting myths from truth”. Many attendees commented on the value of the coping strategies that the seminar introduces.
	b) Understanding symptoms and triggers The detailed exploration of CFS/ME symptoms and their behaviour in the first seminar was reported as beneficial. This included knowing what symptoms are typical for CFS/ME. For some people, this helped them to feel more confident in the diagnosis, and this confirmation was valued.
	c) Understanding the ‘alarm system’ model This explanatory model was helpful for a number of participants, and furthermore a number of patients also commented on the value of the seminars in helping them to feel believed. This sense of validation and of “being believed” was reported as an important benefit from the seminars.
	d) Sleep management The second seminar explored sleep management in depth, and this sleep advice was valued by a number of people. The reduction of arousal before bedtime was specifically mentioned as a benefit of this session.
	e) Activity management and the use of diaries People valued the use of a diary to identify high, medium and low demand activities. By utilizing the diary, people were able to have a visual representation of their daily activities, which led to more awareness of triggers for setbacks. This helped with “keeping on an even keel”, and “avoiding boom and bust" as they are able to reflect on their activities and plan/spread their low, medium and high activities evenly throughout the day, and throughout the week. Help with understanding and setting baselines was also identified as an important outcome of the seminars. Linked with the activity analysis, the value of recuperative rest in achieving stability was identified.
	f) Meeting others: not feeling so alone Attendees commented that meeting others was very useful in that they no longer felt alone. In addition, many participants wrote that it was helpful to hear others’ knowledge and experience: comments included “sharing feelings and knowledge” and “talking to others and sharing experiences”. A few attendees commented in the suggestions section that they would have liked a way of staying in touch with others with CFS/ME, demonstrating the value of being with individuals with the same condition.
	g) The delivery of the seminars Attendees valued the biological and scientific explanations, for example, those used to explain and clarify sleep management. The “warm and accepting atmosphere” and “non-judgemental approach” was important, as was being able to ask questions. The knowledge of the facilitators and their ability to explain clearly was valued. The group participation was also identified as an important part of the delivery as this also contributed to creating a collaborative and accepting atmosphere.
	The most difficult aspects of the Foundation Phase Seminars

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Study	Bristol CFS/ME Service[90]
	a) **Managing symptoms during the seminars** A common difficulty experienced was CFS/ME symptoms during the seminars. These issues included concentrating on the topic being discussed and retaining all the information during the seminar. There were also difficulties reported in sitting upright, and a number of comments were made about the uncomfortable chairs. For some, the lights were too bright, and more than one person reported difficulty staying awake. It seems that the room has been too warm on occasion, and a "lack of fresh air" was also experienced. One attendee thought that the sessions were too long, whereas another thought that a two-hour seminar would be better to allow people to talk more.
	b) **Accessing the seminars** A few attendees expressed that the location of the seminars and the distance they had to travel was an issue. Furthermore, attendees said that managing fatigue in order to attend the seminar has also been an issue for some. Finding a parking space was also difficult for some. 10.30am was experienced as too early in the morning for some. Others found it difficult to manage the seminars in addition to their work duties. One individual reported difficulty in remembering the date and time for the seminar.
	c) **Difficulty putting "Theory into Practice"** A few attendees mentioned that applying the strategies into practice would be difficult as it depends on their work and lifestyle as well as the severity of their CFS/ME. Others also mentioned that in understanding the condition, they became more aware they will have to make changes in their daily life, including "breaking habits" and "facing the necessary changes in lifestyle". In addition, some also mentioned that they are unsure about what happens next after the seminars: "not understanding next steps", "what next?", "applying things learnt - not sure how to start". There was recognition that moving forwards would be a difficult process.
	d) **Problems with a group setting** There were a number of specific issues raised which related to problems with the group setting. One individual commented on the lack of personal focus as being a difficulty with the seminars. One individual reported difficulty in "opening up" in front of the group. One individual commented that it felt as if others were not as severely affected. Two people commented that they would like the information to be shared with their family. There were comments made about some attendees talking more than others and about some negative comments made by others attending the seminars. One person found it difficult that staff were not able to answer individual questions, and that they were guided to speak to their clinician or GP about these issues.
	e) **The emotional impact of the seminars** A number of comments reflected the challenges inherent in confronting the reality of CFS/ME in the seminars. The information about prognosis offered in the seminars was experienced as a difficulty, with one person saying that "improvement in condition not a quick fix", and another saying "there is no simple answer". One person suggested that staff should be more positive about the statistics about recovery rates, and another indicated that it was "depressing at times".
Limitations and applicability of evidence	Severe methodological limitations due to no clear statement of research aim; recruitment strategy and participant characteristics not clearly described; unclear relationship between researchers and participants (analysis conducted by 'three team members').

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Study	Bristol CFS/ME Service[90]
	Moderate concerns regarding applicability due to lack of information on participant characteristics including whether they experience PEM.

Study	Bristol CFS/ME Service[540]
Aim	To gather feedback from patients who were either current or recent patients of NHS CFS/ME Services.
Intervention details	CBT, mindfulness meditation, GET
Population	Patients of the Bristol CFS/ME Service and parents of young people attending the Paediatric CFS/ME Service at Bath.
Setting	Online, UK.
Study design	Survey including closed and open-ended questions and thematic analysis.
Methods and analysis	The primary question was: "Do you think that adults and children with Chronic Fatigue Syndrome or ME (CFS/ME) should have access to specialist NHS services for assessment and treatment?" Response options were yes or no. The survey then invited participants to add free text, if they wanted to say anything else. The main emphasis of the data reported is a thematic analysis of the qualitative data collected.
Findings	**Self-Management support**
	Respondents valued the support from specialist services to learn skills and strategies to self-manage the condition. There were specific mentions of both CBT and Mindfulness meditation as being helpful approaches.
	Criticisms of services
	Out of 612 responses before the 23rd July 2019 (when the survey URL was made available to the public via social media), only three comments criticised CBT and three criticised GET. One comment expressed a concern that CBT and GET were based on poor science, and a second comment suggested that they were harmful and ineffective. One comment expressed concern that some services do not offer medical input. One person was unhappy with the delivery of a group that they attended.
Limitations and applicability of evidence	Moderate methodological limitations due to unclear relationship between researchers and participants (data appears to have been analysed by members of the service); data analysis (unclear methods). Moderate concerns regarding applicability due to lack of information on participant characteristics (including PEM); lack of information on which interventions were received.

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Study	Gladwell 2013[291]
Aim	To explore the experiences of people with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) of rehabilitation therapies so as to build an understanding of reasons for the discrepancy between the notably mixed experiences regarding effectiveness reported in patient surveys and the RCT evidence about the efficacy of Graded Exercise Therapy (GET). To review patient experiences of two related rehabilitation approaches, Exercise on Prescription (EoP) and Graded Activity Therapy (GAT).
Intervention details	Graded exercise therapy (GET), the functionally oriented Graded Activity Therapy (GAT), or Exercise on Prescription (EOP). Respondents had been treated in a range of clinical settings in which there should have been awareness of the NICE Guidelines. The most frequently mentioned location for therapy was the patient's home, but quite often this was in combination with therapy supervision and/or exercise at other locations including GP surgeries, hospital outpatient departments, physiotherapy departments, hydrotherapy pools, specialist units, gyms and recreation centres.
Population	Respondents to 2010 survey of rehabilitation therapies carried out by Action for ME who started rehabilitation during or after 2008 and had tried one of three rehabilitation therapies: GET, the functionally oriented Graded Activity Therapy (GAT), or Exercise on Prescription (EOP). N=76; male/female 14/62; age group <30 years n=19, 30<40 years n=20, 40<50 years n=23, 50+ years n=13; decade of onset 1980s n=7, 1990s n=14, 2000+ n=55
Setting	Online survey, UK
Study design	Thematic analysis of qualitative data submitted as ''free text'' in an online survey.
Methods and analysis	Qualitative data submitted as ''free text'' in the responses to the 2010 survey of rehabilitation therapies carried out by Action for ME. These sections encouraged the respondents to write about their experiences of the rehabilitation therapies, to build a picture of what was helpful and unhelpful about the therapies. The data were analysed using thematic analysis by the first author and a volunteer living with CFS/ME. This entailed reading and re-reading the data to develop a sense of emerging topics, starting with simple flexible themes and working definitions. A paper-based method was used to facilitate shared decision-making. Themes were reviewed to ensure the contextual relevance and comprehensiveness of the developed categories. The data extracts were then linked back to each case and organised within these themes in a matrix then reviewed by all authors.
Findings	**Supportive communication with a therapist**
	Many comments on assessment and ongoing therapist support affirmed the importance of good communication and a supportive approach. Seeing a specialist could be an especially positive experience. An individualised approach was highlighted by some, so that attention could be paid to individual problems such as balance, and so to enable working together to be experienced as having specific meaning for the persons themselves.
	Treatment which included routines and goals

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Study	Gladwell 2013[291]
	Being encouraged to develop a routine was helpful for some. Several related comments suggested the desirability of having a goal to work towards. This was seen by some people as helping define the process as clearly directed at improvement. Other exercise-related benefits were seen as additional to any improvements in health which might include social. Others valued being outdoors in the fresh air and getting away. Being able to move about more was linked to increasing confidence.
	Value attached to baselines and controlled pacing
	Some found the baseline setting and pacing involved in rehabilitation to be helpful in setting realistic and manageable targets for activity. Others conveyed how this worked for developing a process of rehabilitation. Some identified the new skills that they gained in identifying aspects of their activity. Several participants described the sense of specific control of activities that could then be gained.
	Poor communication and support
	Negative comments on the assessment, or ongoing therapist support, were often indicative of poor communication and feelings of being unsupported. Some emphasised how their opinions were not taken into account. Many described this as not being responded to in context. Some experienced miscommunication. Many of these reported trying in vain to convey to therapists their sense that GET was not successful.
	Conflict in beliefs about ME and rehabilitation
	A particular difficulty reported by several respondents, centred on therapist-patient differences in beliefs about the nature of their condition and the role of rehabilitation. Some of these conflicts were about a diagnosis of ME versus that of CFS or Post-Viral Fatigue Syndrome, with consequences for the appropriateness of treatment and expertise of therapists needed to provide this. Others focused on the likely harmful effects of exercise in ME compared with other fatigue-related illnesses. Some emphasised their view that ME was largely misunderstood by health professionals. One saw this as a lack of therapist interest in gaining the necessary accurate and specific knowledge about ME.
	Pressure to comply with treatment
	Several reported feeling unreasonably pressured to comply with the rehabilitation therapy. Such pressure might include recording patients' reluctance to comply as a formal refusal of treatment. A key pressure experienced as problematic was where patients were asked to ignore their symptoms and to continue trying to do more activity than they felt was sensible. This was found especially problematic when people experienced setbacks in treatment, but were given advice to ‘‘push through”. Others felt that where they had built an understanding of how to successfully self-manage their exercise in relation to their condition, they were still pushed.
	Worsening of symptoms
	Some people reported how worsening symptoms after each session put them off continuing with the therapy. For some, these effects of worsening their symptoms meant they were prevented from doing anything for a long time. For others, the worsening of symptoms meant specifically increased pain which made continuing therapy too difficult. Several reported that their trying to persist with rehabilitation led to a worsening of their symptoms in the longer term, perhaps a year or more.
	Baselines experienced as unsustainable

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Study	Gladwell 2013[291]
	Some respondents clearly did not experience even the baseline levels they had been set as sustainable. This linked with reports of problems following initial exercise testing. Yet, such initial exercise is not required for setting baselines. A recurring theme across reports was the level of exercise being selected by the therapist and experienced by patients as too difficult.
	Feeling blamed for rehabilitation not working
	Some found that difficulties arose or were exacerbated in their relationship with the therapist when they reported finding the therapy unhelpful, and the blame was shifted onto them. One person reported that the therapist could not comply, were their assumed lack of effort. Another respondent described then even feeling guilty for being physically ill.
Limitations and applicability of evidence	Minor methodological limitations due to recruitment strategy (single ME charity; may be more likely to have not improved/recovered; unclear consideration of ethical issues). No concerns regarding applicability. PEM reanalysis: moderate concerns regarding applicability due to participants being a self-selected sample for which PEM was unclear.

Study	Yorkshire Fatigue Clinic[581]
Aim	To learn from the experiences of patients as part of improving quality of care in an area of healthcare that remains controversial and unpopular with many suffers.
Intervention details	The focus of the service is on individualised care and tailored rehabilitation programmes based on individual patient needs. The service works with adults and young people aged over 13 years of age. The clinical team (2.7 WTE) includes four part-time occupational therapists and a GP with Special Interest. The service does not use a specific treatment regime, such as CBT or GET. The therapy programme is focused on the impact of the illness on dysregulation of biological systems, such as autonomic regulation and homeostasis. The programme uses rehabilitation strategies to work on stabilising the condition and then working on graded increases to tolerance levels for physical, cognitive, and social activities. For example, this may include stabilising orthostatic tolerance through fluid intake, use of compression and heart rate regulation and then gradual increases in changes to positions against gravity. Consequently, although components of condition specific research-based regimes, such as CBT and GET may be involved the intention of how they are used and the process of applying them is different to these manualised therapies. Also, these components are only part of a much broader rehabilitation approach that includes aspects of other therapies, such as energy conservation, sensory integration, ergonomics, heart rate training, sleep management, vocational rehabilitation, and compassion-based therapies. Patients with more severe symptoms may stay in the stabilisation phase, with a focus on sleep and eating patterns, improving quality of rest and orthostatic control for a prolonged period before they are able to grade any activity tolerance without causing post exertional malaise.

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Study	Yorkshire Fatigue Clinic[581]
	The assessment process in the service will include either a medical or therapy assessment consultation, attendance at an Introductory Workshop for the patient and carer/family member or parents, and a follow up or care planning session. Those patients who are then suitable for rehabilitation will be offered a group programme or individual sessions, which can be provided by face to face contact, by telephone or telemedia. The group sessions focus on stabilisation over four fortnightly sessions and then an individual review, followed by four monthly sessions focused on tolerance and another individual review. The individual sessions are usually monthly, and the average number is ten sessions. This programme is deliberately protracted over a longer time duration due to the fluctuating nature of the illness and the importance of supporting people through learning how to manage relapses. Severe and very severely affected patients receive sessions at home on the frequency they prefer / can tolerate or by telemedia (if outside of the locality). The patient may not be able to undertake rehabilitation due to other life demands and not having the capacity at that point in time to focus on a programme. Some patients feel they have found the optimum way to manage their condition and make the choice not to undertake a rehabilitation programme if they feel it will not be of benefit to them, which is different to non-compliance.
Population	N=252
Setting	Online survey, UK
Study design	Routinely administered online patient surveys
Methods and analysis	Anonymous survey of patient experience. The patient is automatically sent an e-mail with the link to the survey by the electronic patient admin system when the treatment episode is closed on the system. The patient completes the survey on-line with no identifiable information. This is so that patients can be assured that any negative feedback will have no impact on future care and can give their opinions freely. Patients were given the opportunity to provide qualitative feedback in relation to four open questions. These questions were: what did you find most helpful/beneficial, what did you find least helpful, what could we change or improve and any other feedback. The results of the questionnaire were automatically collated by the Survey Monkey programme. A thematic analysis was completed.
Findings	**Access/environment** Participants found the travel required to access the clinic and carpark to be least helpful/beneficial.
	Session content Participants requested less medical content, more nutrition and group material making individual references.
	Sessions and structure Participants referred to waiting time as a less beneficial/helpful aspect, others referred to having more sessions and changing session lengths.
	Staffing Participants found staff support, knowledge and individual approaches helpful/beneficial. Team members were referred to, including additional members of the multi-disciplinary team and having more staff. Participants wanted nutritionist support and counselling services to be provided.
	Self-knowledge

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Study	Yorkshire Fatigue Clinic[581]
	The self-knowledge that participants gained allowed them to develop tools in their recovery.
	Recovery Recovery was a common theme with subthemes such as hope, and goals attained for individuals including wellness and achieving work. Participants reported their progress with individual goals and feeling in more control.
	Diagnosis and validation Obtaining a diagnosis and validation of symptoms was a key process with some patients describing this as the most beneficial aspect of the service.
	Signposting Some participants referred to the signposting process as a beneficial aspect to the service.
	Resources and therapy structure Participants referred to the resources and therapy structure with subthemes such as hearing others' stories and social group gatherings.
Limitations and applicability of evidence	Severe methodological limitations due to recruitment strategy (participants sent the survey once the treatment episode is closed on the system); unclear relationship between researchers and participants (analysis appears to have been carried out by service team members); unclear methods of data analysis; no clear statement of findings. Moderate concerns regarding applicability due to lack of information on participant characteristics including whether they had PEM.

Study	Physios for ME[588]
Aim	Not reported
Intervention details	Physiotherapy
Population	N=441 people with ME (53% had experienced physiotherapy)
Setting	Online, UK
Study design	Online survey
Methods and analysis	Using a survey question on the ME Association website, people with ME were asked about their experiences of Physiotherapy. People with ME were also asked to either email, tweet or message on facebook telling about their experiences in more detail.
Findings	**For people who had a positive experience of physiotherapy, physiotherapist was praised for positive personal attributes.**
	For people who had a positive experience of physiotherapy, treatment was tailored to the individual.
	For people who had a negative experience of physiotherapy, physiotherapist had negative personal attributes

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Study	Physios for ME[588]
	For people who had a negative experience of physiotherapy, encounter with physiotherapist was unhelpful.
	For people who had a negative experience of physiotherapy, lack of understanding from physiotherapist.
	For people who had a negative experience of physiotherapy, GET was mentioned.
Limitations and applicability of evidence	Severe methodological limitations due to no clear statement research aim; recruitment strategy (single ME charity; may be more likely to have not improved/recovered; unclear intervention details); no information on method of qualitative data analysis; key themes only with no data presented to support findings. Moderate concerns regarding applicability due to lack of information on participant characteristics or interventions. PEM reanalysis: serious concerns regarding applicability due to a lack of information on participant characteristics, including PEM, and lack of information on the interventions received.

Study	De Carvalho Leite 2011[220]
Aim	To produce and to facilitate epidemiological and social research, in response to the needs of people with CFS/ME in England so as to fill a major gap in the evidence of the occurrence and the impact of this disease.
Intervention details	Various.
Population	Adults (18 years and older) with CFS/ME in England. Researchers contacted relevant support groups, community organisations and centres, practitioners, and media to publicise the CFS/ME Observatory and the study across England. Six of the 35 participants were purposively selected (to include a diverse range of illness severity, duration and social variation) for both an initial focus group discussion as well as later one-to-one interviews with a researcher. The other 29 were invited to take part in one-to one interviews only. N=35; male/female 8/27; age 18-25 years (n=4), 26-40 years (n=8), 41-55 years (n=15), 56+ years (n=8)
Setting	Participants' homes, UK.
Study design	Semi-structured interviews and thematic analysis
Methods and analysis	Data elicited through focus group discussion and the one-to-one interviews were descriptions of experiences, beliefs and feelings about living with CFS/ME and being managed within health and social care services in England. These were tape-recorded and transcribed. The focus group with six people with CFS/ME was used to identify the main themes and issues to be explored more deeply in the subsequent interviews. It took place in a quiet room and lasted for two hours, with a break for refreshment and rest. The group was conducted by a researcher, while another researcher supported the group dynamics, observed and took notes to facilitate later analysis. The sequence and wording of questions were decided in the course of the discussion to respond to participants' preferences and conversational styles. One-to-one semi-structured interviews of about 45 minutes (up to a maximum of 3 interviews per participant,

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Study	De Carvalho Leite 2011[220]
	45 interviews in total) were conducted with the 35 participants by a researcher at the participant's home or another place convenient for them. Thematic analysis was used. The focus group data transcript was analysed by four researchers, who identified the main emerging thematic areas and then adapted the question guides for the one-to-one interviews. The one-to-one interview transcripts were analysed by five researchers drawing on the inductive approach. They first independently read and re-read the transcripts to identify and extract words and text sections. They independently selected, focused and condensed the data with codes linked to text 'chunks' and pre-analytic remarks used to establish a preliminary code system which yielded many themes. Following the initial development of the preliminary coding system, three researchers met to compare the reliability of codes and to agree the developed coding scheme. Before comparative subject analyses were carried out, these researchers developed new codes emerging during further individual analysis which included a richer variety of experiences of living CFS/ME and services and to ensure data saturation. Finally, a wider group of researchers drew conclusions for the whole dataset by identifying themes or patterns, contrasts, clarifying relationships and building an interpretative understanding from the set of narratives. Study results were shared with participants to check whether their expressed main views were included, to be amended to take account of their response (respondent validation). The draft report was reviewed by the steering group and reference group of the CFS/ME Observatory, with members of the CFS/ME community and other stakeholders to also inform the report (member checking) and there were dissemination events to share key findings with CFS/ME community members to check their perceived relevance (member validation).
Findings	**Alternative therapies** Participants desperate for relief of feelings of pain or illness reported finding treatments such as massage, osteopathy, dietary advice and acupuncture helpful, and it caused ongoing frustration that such interventions were not funded by either the NHS or by private health insurance for CFS/ME. Citations show these as especially likely to be mentioned by participants from ethnic minorities.
	Limited time for consultations Some participants highlighted the limited time for consultations as a barrier to appropriate care provision and another reason for seeking support outside the NHS. For example, one participant explained that her NHS acupuncturist limited treatment to only three needles, whilst the private service she eventually attended but could only afford for a limited time allowed the acupuncturist time for enough needles for pain relief and to discuss her situation.
Limitations and applicability of evidence	No significant methodological limitations noted. Moderate concerns regarding applicability due to different research aim and limited detail on interventions received. PEM reanalysis: serious concerns regarding applicability due to existing reasons and it being unclear if participants had PEM.

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Study	McManimen 2019[497]
Aim	To analyze the ME and CFS patient perspective and further elucidate this underserved population and any issues in the doctor-patient relationship that may be leading patients to perceive HCPs as dismissive.
Intervention details	Various
Population	Individuals at least 18 years of age and able to read and write in English self-reporting a diagnosis of ME or CFS, recruited through a variety of methods including postings on social media websites, patient advocacy newsletters, and internet forums, as part of a larger study. N=464
Setting	Online, USA
Study design	Online survey including closed and open-ended questions and thematic analysis.
Methods and analysis	The questionnaire was completed using Research Electronic Data Capture (REDCap), an online survey tool. Participants (N = 541) were asked, “Have you ever experienced a dismissive attitude from a health care professional?” Those who answered “Yes” (89.4%) were then prompted with the following open-ended question: “Please describe this experience.” Participant responses (N= 464) were thematically coded and analyzed using NVivo software. Qualitative responses were coded using an inductive and iterative approach. First, authors familiarized themselves with the data through repeated readings. The first 100 responses were read individually and authors noted recurring ideas and possible themes. Initial major themes and subthemes were generated after the authors met and organized their notes into meaningful categories, creating a preliminary codebook. Using the codebook researchers each coded a proportion of the responses and updated the codebook as authors clarified themes. Researchers met to discuss differences in coding and the codebook was updated as necessary. For themes where agreement was moderate or below, the authors clarified the definition of the code. Each time the codebook was updated, the authors went back through previously coded responses and recoded based on the updated guidelines until good reliability was attained.
Findings	**Physical activity** Participant descriptions of their interactions with HCPs suggested that some of these professionals misinterpreted findings related to pacing and/or suggested harmful physical activity. Some participants described how their HCP told them to ignore the symptoms they came to interpret as warning signs and push themselves beyond their comfort level. Others described attempting to tell their HCP that GET made them physically worse or that psychological treatment was not helping, but their concerns and viewpoints were often dismissed.
Limitations and applicability of evidence	No significant methodological limitations noted. Moderate concerns regarding applicability due to different research aim (analysis based only on those who had experienced a dismissive attitude from a health care professional) and limited detail on interventions received.

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Study	McManimen 2019[497]
	PEM reanalysis: serious concerns regarding applicability due to existing reasons and it being unclear if participants had PEM.

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Appendix E Qualitative evidence summary

Adults (severity mixed or unclear)

Table 124: Summary of evidence: Cognitive behavioural therapy

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
Hopes and expectations					
1	Semi-structured interviews	Feelings of confusion and apprehension at the beginning of therapy were replaced by feeling as ease. Some felt that the treatment exceeded expectations.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Validation					
1	Semi-structured interviews	Treatment was perceived as a source of validation. CBT helped people to feel understood and to reaffirm that their suffering is real and recognised.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
CBT as support					
1	Semi-structured interviews	The simple act of talking to someone was of benefit and people were comforted by the knowledge that the therapist was available if they needed help as a form of safeguard.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Relationship with the therapist					
1	Semi-structured interviews	People valued building a relationship with the therapist and reported a preference for face-to-face consultations, which were found by some to be more personal and enabling.	Limitations	Moderate concerns about methodological limitations[a]	LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [a]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Personalised care					
1	Semi-structured interviews	People felt that treatment was shaped by both the client and the therapist, which made them feel in control and able to contribute.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [a]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Motivation and engagement					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi-structured interviews	People recognised that they must be ready to invest effort and motivation must come from within. However, this might depend on illness severity and personal circumstances at the time.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Self-monitoring/management support					
2	Semi-structured interviews (1 study), survey including closed and open-ended questions (1 study)	Improvement was closely linked to a mastery of self-monitoring. People valued the support to learn skills and strategies to self-manage, specifically through CBT and mindfulness meditation approaches.	Limitations	Moderate concerns about methodological limitations[b]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [b]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	No or very minor concerns about adequacy	
Behavioural aspects					
1	Semi-structured interviews	Behavioural tasks such as activity or sleep monitoring were found to be helpful in facilitating the development of self-awareness.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Cognitive aspects					
1	Semi-structured interviews	Feedback on the cognitive aspects was mixed, with some perceiving it as crucial and others finding it less useful, especially for physical symptoms.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance (PEM)	Moderate concerns about relevance [a]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Negative perceptions					
1	Unstructured interviews	Some perceived CBT as controlling, patronising and a form of brainwashing.	Limitations	Moderate concerns about methodological limitations[c]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[c]	PEM reanalysis:
			Relevance (PEM)	Serious concerns about relevance [c]	VERY LOW
			Adequacy	Minor concerns about adequacy[c]	
Effect on symptoms					
3	Semi-structured interviews (1 study), survey including closed ended and open-	Response was mixed, with some reporting a gradual improvement which did not reach a pre-morbid level of functioning, some reporting no change and some reporting a worsening of symptoms. There were criticisms of the therapy being used as a 'treatment' for ME.	Limitations	Moderate concerns about methodological limitations[d]	LOW
			Coherence	Moderate concerns about coherence[d]	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	ended questions (2 studies)		Relevance (PEM)	Moderate concerns about relevance [d]	VERY LOW
			Adequacy	No or very minor concerns about adequacy	
Ongoing support					
1	Semi-structured interviews	Many felt they would have liked the support of additional sessions; many feared a relapse and did not know how they would cope without CBT.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	

[a]*One study with moderate methodological limitations due to only participants who had completed treatment being recruited, unclear relationship between the researcher and participants and unclear consideration of ethical issues (Picariello 2017); minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: moderate concerns about relevance with participants fulfilling diagnostic criteria where PEM was not compulsory (Picariello 2017).*

[b]*Two studies with moderate methodological limitations due to only participants who had completed treatment being recruited and unclear consideration of ethical issues in one study (Picariello 2017), unclear methods of data analysis in one study (NHS North Bristol, 2019) and an unclear relationship between the researcher and participants in both studies (Picariello 2017; NHS North Bristol 2019); PEM reanalysis: moderate concerns over relevance with moderate concerns in one study with participants fulfilling diagnostic criteria where PEM was not compulsory (Picariello 2017) and serious concerns in the other study due to a lack of information on participant characteristics including PEM and a lack of information on which interventions were received (NHS North Bristol 2019)..*

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[c]One study with moderate methodological limitations due to recruitment through ME/CFS charities, unclear interventions and insufficient data presented to support all findings (Ward 2008); minor concerns regarding relevance due to unclear interventions; minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: serious concerns regarding relevance due to unclear interventions (finding relates to interventions which participants perceived to be CBT, but no details) and diagnosis made by a medical practitioner, but with no information on PEM (Ward 2008).
[d]Two studies with moderate methodological limitations due to only participants who had completed treatment being recruited, unclear relationship between the researcher and participants and unclear consideration of ethical issues (Picariello 2017), recruitment through ME/CFS charities and issues regarding methods of data collection and analysis (Oxford Clinical Allied Technology and Trials Services Unit 2019) and one study with serious methodological limitations due to unclear interventions, recruitment through an ME/CFS charity, unclear consideration of ethical issues, unclear methods of data analysis and no clear statement of some findings (Leary 2019); moderate concerns about the coherence of the finding with one study reporting worsening of symptoms (Oxford Clinical Trials Services Unit 2019) and the other two reflecting subtle or minimal differences (Picariello 2017; Leary 2019); PEM reanalysis: moderate concerns over relevance with moderate concerns across contributing studies due to lack of details on diagnosis and PEM being self-reported in one study (Leary 2019), with participants fulfilling diagnostic criteria where PEM was not compulsory in one study (Picariello 2017) and diagnosis made by a clinician but the percentage of participants who had PEM being self-reported in the third contributing study (Oxford Clinical Allied Technology and Trials Services Unit 2019).

Table 125: Summary of evidence: other psychological therapies (counselling)

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Activity related counselling interventions					
1	Unstructured interviews	Pacing was the most valued aspect, although in the early stages, people often got this wrong, resulting in periods of crushing fatigue and pain. There was often a delay before the full impact of activity was felt and for these people, exercise regimes and sometimes activity programmes were viewed negatively. People often felt pushed to overdo it, leading to significant relapse.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Stress-management counselling interventions					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Unstructured interviews	Relaxation and meditation techniques were viewed positively, with people talking of reduced stress levels in terms of the impact of their condition and their life activities.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Thought management counselling interventions					
1	Unstructured interviews	Responses to thought management strategies were mixed. Some found suggestions of negative thoughts being counterproductive to be patronising and negative; some found such notions simplistic; some found the interventions useful, for example in helping them to counter unrealistic or catastrophizing reactions.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Examining the influence of the past counselling interventions					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Unstructured interviews	Very few people experienced this approach. Those who had felt very negatively about it because they thought the suggestion was that the cause of their ME might be rooted in the past and they firmly rejected any psychological cause for their condition.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Relationship with the therapist					
1	Unstructured interviews	Positive reflections involved counsellor listening, understanding and offering appropriate challenge, whereas negative reactions to counsellors involved poor communication and non-empathic responding.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	
Physical impact					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Unstructured interviews	Several people mentioned the physical impact of counselling on someone with severe ME, describing the difficulty of making their way to and from the session each week and the strain of keeping up a session of 50 minutes.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[a]	

[a]*One study with moderate methodological limitations due to recruitment through ME/CFS charities, unclear interventions based on participant recall and insufficient data presented to support all findings (Ward 2008); minor concerns about relevance due to unclear interventions in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study.*
[b] *Serious concerns about relevance due to unclear interventions in the contributing study and it being unclear if participants had PEM.*

Table 126: Summary of evidence: Graded exercise therapy/other exercise interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Baseline activity levels and false starts					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
2	Semi structured interviews (1 study), qualitative data submitted as "free text" in an online survey (1 study)	Most people found stabilising their routine, choosing physical activity and setting their baseline level to be straightforward, but baseline levels were not experienced as sustainable. Some experienced 'false starts' as they commenced the programme.	Limitations	Minor concerns about methodological limitations[a]	MODERATE
			Coherence	Minor concerns about coherence[a]	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	Minor concerns about relevance[a]	
			Adequacy	No or very minor concerns about adequacy	
The indeterminate phase of GES					
2	Semi-structured interviews	Most people noticed no immediate difference in symptoms, or an exacerbation during the initial phase which resulted in them not knowing if the programme was helping or hindering their condition and during this 'indeterminate phase', it was found to be difficult to maintain motivation.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[b]	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	Minor concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[b]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
Too difficult					
3	Semi-structured interviews (2 studies), qualitative data submitted as "free text" in an online survey (1 study)	Most found following the programme to be 'hard work'. The level of exercise was selected by the therapist and experienced by patients as too difficult.	Limitations	Minor concerns about methodological limitations[c]	LOW
			Coherence	Minor concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	
			Relevance (PEM)	Moderate concerns about relevance [c]	PEM reanalysis: LOW (no change)
			Adequacy	Minor concerns about adequacy[c]	
'Push-crash' and worsening of symptoms					
6	Semi-structured interviews (2 studies), focus groups (1 study), survey including closed ended and open-ended questions (2	People experienced a lack of control over their bodies after exertion subsequent to non-customised activity. For some, debilitating exacerbations of symptoms were a reason for discontinuation. For others, trying to persist with rehabilitation led to a worsening of their symptoms in the longer term.	Limitations	Moderate concerns about methodological limitations [d]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Relevance (PEM)	Moderate concerns about relevance [d]	PEM reanalysis:

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	studies), qualitative data submitted as "free text" in an online survey (1 study)		Adequacy	No or very minor concerns about adequacy	LOW
Competing commitments					
1	Semi-structured interviews	People needed enough 'capacity' in their lives to experience an exacerbation of symptoms and for this not to interfere with essential life activities. Higher functioning participants had more to do in their lives and reported more challenges in fitting the programme in to busier lifestyles.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance[e]	
			Adequacy	Minor concerns about adequacy[e]	
Comorbid conditions					
1		People who reported their condition to be 'a little worse' following treatment reported more comorbid conditions and greater	Limitations	No or very minor concerns about	MODERATE

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	Semi-structured interviews	interferences from these conditions when following the programme.		methodological limitations	
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance [e]	
			Adequacy	Minor concerns about adequacy[e]	
Therapist approach					
4	Semi-structured interviews (2 studies), qualitative data submitted as "free text" in an online survey (2 studies)	Approaches and attitudes taken by physiotherapists that were enthusiastic, gentle, understanding and patient centred generally facilitated a positive experience and engagement with them and the programme. Conversely miscommunication and not having their opinions taken into account left people feeling unsupported.	Limitations	Minor concerns about methodological limitations[f]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[f]	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concern about relevance[f]	
			Adequacy	No or very minor concerns about adequacy	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Conflict in beliefs					
1	Qualitative data submitted as "free text" in an online survey	There were therapist-patient differences in beliefs about the nature of their condition and the role of rehabilitation with consequences for the appropriateness of treatment and expertise of therapists needed to provide this.	Limitations	Minor concerns about methodological limitations[g]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [g]	
			Adequacy	Minor concerns about adequacy[g]	
Pressure to comply with treatment					
2	Qualitative data submitted as "free text" in an online survey	People felt unreasonably pressured to comply with the rehabilitation therapy, especially when asked to ignore symptoms and continue trying to do more activity than they felt was sensible. People tried in vain to convey to therapists their sense that GET was not successful.	Limitations	Minor concerns about methodological limitations[h]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[h]	PEM reanalysis:
			Relevance	Serious concerns about relevance [h]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	No or very minor concerns about adequacy	LOW
Feeling blamed					
1	Qualitative data submitted as "free text" in an online survey	Some experienced difficulties in their relationship with the therapist when they reported finding the therapy unhelpful, and the blame was shifted onto them.	Limitations	Minor concerns about methodological limitations[g]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [g]	
			Adequacy	Minor concerns about adequacy[g]	
Booklet information resource					
1	Semi-structured interviews	Some found the information booklet helpful, whereas others found it patronising, having the feel of marketing material or seemingly designed for participants with a higher level of functioning. The statement suggesting that there should be no ill effects from the programme was not accurate in their experience.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy [e]	
Personalised care					
4	Semi-structured interviews (1 study), focus groups (1 study), qualitative data submitted as "free text" in an online survey (2 studies)	Being allowed to choose activities supported motivation and individually adapted advice was perceived to be helpful. People described experiences of becoming extremely ill after organised exercise, whereas similar exercise undertaken in a non-organised way was helpful, enjoyable and easier to adapt to individual energy level.	Limitations	Moderate concerns about methodological limitations[i]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[i]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [i]	
			Adequacy	No or very minor concerns about adequacy	
Overall approach					
1	Semi-structured interviews	Some felt that the remit of graded exercise self-help was too narrow and that it needed a broader approach which included CBT or took into account mental activity.	Limitations	No or very minor concerns about methodological limitations	MODERATE

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy [e]	
Knowledge and understanding					
1	Semi-structured interviews	An understanding of the theory behind graded exercise helped understanding and engagement in the programme.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[e]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Support for self-management					
2	Focus groups (1 study), qualitative data submitted as "free text" in an online survey (1 study)	Reviewing the daily workload with an occupational therapist, baseline setting and pacing was found to be helpful. Mapping exercises helped to prioritise tasks and reviewing activities, putting expectations aside and letting things happen diminished stress.	Limitations	Moderate concerns about methodological limitations[j]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[j]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance [j]	
			Adequacy	No or very minor concerns about adequacy	
Routines and goals					
1	Qualitative data submitted as "free text" in an online survey	Some found treatments that encouraged development of routines and setting of goals to be helpful.	Limitations	Minor concerns about methodological limitations[g]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [g]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy[g]	
Additional benefits					
1	Semi-structured interviews	Social benefits of group exercise were found to be extremely important and encouraged attendance and compliance. Additional benefits were enjoyment, better ability to self-manage, increased fitness or use of muscles, enhanced breathing, regulation of body temperature, the engaging mixture and pacing of exercises and improved cognitive symptoms.	Limitations	Minor concerns about methodological limitations[k]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[k]	
			Relevance (PEM)	Serious concerns about relevance [k]	
			Adequacy	Minor concerns about adequacy	
Practical limitations					
1	Semi-structured interviews	Aspects of an aquatic exercise intervention that some participants did not like included travelling, the time it took to get undressed and dressed, the energy needed to remove wet swimsuits and heart rate monitors, the discomfort of wearing a heart rate monitor and the possible need for more space in the pool.	Limitations	Minor concerns about methodological limitations[k]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[k]	PEM reanalysis:
			Relevance (PEM)	Serious concerns about relevance [k]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy	VERY LOW
Other sources of support					
1	Semi-structured interviews	People with who reported their condition to be 'much better' following treatment reported use of other complementary therapies such as counselling, CBT, self-help or peer support.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: MODERATE (no change)
			Relevance (PEM)	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[e]	

[a]*One study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014) and very minor limitations in one study due to unclear consideration of ethical issues (Cheshire 2020); minor concerns about the coherence of the finding, with some description related to ease and benefits of setting baselines (Gladwell 2014) and some related to unsustainability and 'false starts' (Cheshire 2020); PEM reanalysis: minor concerns about relevance with moderate concerns over one study due to participants being a self-selected sample and it was unclear if they experienced PEM (Gladwell 2014) and no concerns over the other contributing study (Cheshire 2020)*

[b]*Minor concerns regarding relevance due to one study only including female participants (Broadbent 2020) and no concerns regarding the other study (Cheshire 2020); minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but mainly based on one study; PEM reanalysis: minor concerns regarding relevance with serious concerns in one study due to unclear PEM and the study only including female participants (Broadbent 2020) but no concerns in the other contributing study (Cheshire 2020) and the majority of the information supporting the theme coming from the study with no concerns.*

[c]*Two studies with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014), unclear relationship between researchers and participants and data analysis (Broadbent 2020) and very minor limitations in one study due to unclear consideration of ethical issues (Cheshire 2020); minor concerns about the coherence of the finding, with it being unclear whether 'hard work' reported in one study (Cheshire 2020) has the same meaning as 'too*

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difficult' reported in the other (Gladwell 2014) and concerns regarding one study reporting participants wanting longer/more frequent sessions being explained by differences in the type of exercise intervention (Broadbent 2020); minor concerns about adequacy as the evidence is not sufficiently deep (no elaboration or examples in any of the contributing studies); PEM reanalysis: moderate concerns about relevance with moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014), serious concerns in one study due to unclear PEM and the study only including female participants (Broadbent 2020) and no concerns in the other contributing study (Cheshire 2020)

[d]Two studies with moderate methodological limitations due to recruitment through ME/CFS charities, issues regarding methods of data collection and analysis (Oxford Clinical Allied Technology and Trials Services Unit 2019), recruitment through self-selection and clinic staff and unclear relationship between researcher and participants (Larun 2011); one study with serious methodological limitations due to unclear interventions, recruitment through an ME/CFS charity, unclear consideration of ethical issues, unclear methods of data analysis and no clear statement of some findings (Leary 2019); two studies with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014), unclear relationship between researchers and participants and data analysis in the other study (Broadbent 2020); one study with no or very minor limitations (Cheshire 2020); PEM reanalysis: moderate concerns about relevance with serious concerns in two studies due to one study including only female participants and it being unclear if they had PEM (Broadbent 2020) and one study including participants with unclear PEM and conducted in a rural area raising concerns over the applicability of the setting (Larun 2011), but moderate concerns in three studies due to participants being a self-selected sample and it being unclear if they had PEM in one study (Gladwell 2014), due to PEM being unclear or self-reported (Oxford Clinical Allied Technology and Trials Services Unit 2019; Leary 2019) and no concerns in one contributing study (Cheshire 2020).

[e]Minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only mainly based on one study.

[f]Two studies with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014), unclear relationship between researchers and participants and data analysis (Broadbent 2020); one study with very minor limitations due to unclear consideration of ethical issues (Cheshire 2020); one study with serious methodological limitations due to no clear statement of research aim, recruitment through a ME/CFS charity, unclear relationship between researcher and participants, unclear consideration of ethical issues, no information on method of qualitative data analysis and key themes only with no data presented to support findings (Physios for M.E.); minor concerns regarding relevance due to a lack of information on participant characteristics and interventions in one study (Physios for M.E.) and one study only including female participants (Broadbent 2020); PEM reanalysis: moderate concerns regarding relevance with serious concerns in two studies due to a lack of information on participant characteristics including PEM but also on the interventions received in one study (Physios for M.E.) and due to unclear PEM and the study only including female participants (Broadbent 2020) but moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014) and no concerns in the fourth contributing study (Cheshire 2020).

[g] One study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014); minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: moderate concerns over relevance with participants being a self-selected sample and it being unclear if they had PEM (Gladwell 2014)

[h]One study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014) and one study with no or very minor limitations (McManimen 2019); minor concerns about relevance due to one study with a different research aim and limited detail on interventions (McManimen 2019); PEM reanalysis: serious concerns about relevance with moderate concerns in one study with participants being a self-selected sample and it being unclear if they had PEM (Gladwell 2014) and serious concerns in the other study due to limited detail on interventions and concerns over the relevance of the population with the analysis being based only on people who had experienced a dismissive attitude from a health care professional and whose diagnosis and experience of PEM were self-reported rather than confirmed by specific criteria or professional (McManimen 2019).

[i]One study with serious methodological limitations due to no clear statement of research aim, recruitment through a ME/CFS charity, unclear relationship between researcher and participants, unclear consideration of ethical issues, no information on method of qualitative data analysis and key themes only with no data presented to support findings (Physios for M.E.); one study with moderate methodological limitations due to recruitment through self-selection and clinic staff and unclear relationship between researcher and participants (Larun 2011); one study with minor methodological limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014) and one study with very minor limitations due to unclear consideration of ethical issues (Cheshire 2020); minor concerns regarding relevance, with one study having a different aim to the review question (Larun 2011) and a lack of information on participant characteristics and interventions in another (Physios for M.E.); PEM reanalysis: moderate concerns regarding relevance, with serious concerns in two studies due the inclusion of participants with unclear PEM and one study being conducted in a rural area raising concerns over the applicability of the setting (Larun 2011) and a lack of information on participant characteristics including PEM but also on the interventions received in

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one study (Physios for M.E.) but moderate concerns in one study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014) and no concerns in the other contributing study (Cheshire 2020)

[j]*One study with moderate methodological limitations due to recruitment through self-selection and clinic staff and unclear relationship between researcher and participants (Larun 2011) and one study with minor limitations due to recruitment through a single ME/CFS charity and unclear consideration of ethical issues (Gladwell 2014); minor concerns regarding relevance due to one study having a different aim to the review question (Larun 2011); PEM reanalysis: serious concerns over relevance due to serious concerns in one study contributing the majority of the information to this theme as it included participants with unclear PEM and was conducted in a rural area raising concerns over the applicability of the setting (Larun 2011) and moderate concerns in the other contributing study with participants being a self-selected sample and it was unclear if they had PEM (Gladwell 2014)*

[k]*One study with minor limitations due to unclear relationship between researchers and participants and data analysis in the other study (Broadbent 2020); moderate concerns regarding relevance due to the contributing study only including female participants (Broadbent 2020); PEM reanalysis: Serious concerns regarding relevance due to unclear PEM and the contributing study only including female participants (Broadbent 2020).*

Table 127: Summary of evidence: Education/information interventions

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Validation					
2	Semi structured interviews (1 study), service evaluation forms (1 study)	The provision of reliable evidence-based information meant that their GP was validating people's CFS/ME, which enabled them to self-manage their condition. People appreciated meeting health care professionals with knowledge of CFS.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[a]	PEM reanalysis: LOW (No change)
			Relevance (PEM)	Moderate concerns about relevance [a]	
			Adequacy	No or very minor concerns about adequacy	
Knowledge and understanding					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
3	Semi structured interviews (1 study), focus groups (1 study), service evaluation forms (1 study)	Learning about the diagnosis, symptoms, possible causes and prognosis increased understanding and confidence. DVD case studies helped people to understand that others shared their experiences, and the format allowed those who found it difficult to read to access the information. As a result of this information some patients felt that they needed to visit their practice less frequently. It was considered helpful to learn that deterioration may occur even when doing everything 'right'.	Limitations	Minor concerns about methodological limitations[b]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[b]	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [b]	
			Adequacy	No or very minor concerns about adequacy	
Sources of information					
2	Semi structured interviews (1 study), focus groups (1 study)	An evidence-based source of information was welcomed due to issues with identifying reliable information on the internet. Some felt more able to assess information about the illness and treatments more critically.	Limitations	Minor concerns about methodological limitations[c]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance [c]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	No or very minor concerns about adequacy	
Acceptance					
1	Focus groups	Some people with ME/CFS realised that they had to focus on acceptance and coping with the illness rather than curing it. People experienced increased acceptance, although at times still felt that acceptance was equivalent to giving up hope of getting better.	Limitations	Minor concerns about methodological limitations[d]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [d]	LOW
			Adequacy	Minor concerns about adequacy[d]	
Coping					
2	Focus groups (1 study), service evaluation forms (1 study)	People found it especially helpful to learn about pacing and energy conservation, relaxation exercises, how to deal with difficult feelings, economic and public support systems, nutrition and sleep management. They experienced better coping with their illness and increased feeling of control but did not experience better health.	Limitations	Minor concerns about methodological limitations[e]	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance (PEM)	Moderate concerns about relevance [e]	LOW
			Adequacy	No or very minor concerns about adequacy	
Activity management and diaries					
1	Service evaluation forms	People valued the use of a diary, which gave people a visual representation of their daily activities, which led to more awareness of triggers for setbacks. Help with understanding and setting baselines was also identified as an important outcome.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Difficulties accessing and engaging in seminars					
1	Service evaluation forms	Practical issues related to location, environment, timing and duration made accessibility and engagement difficult for some. Managing fatigue in order to attend the seminar was also an issue for some and a common difficulty experienced was CFS/ME symptoms during the seminars.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Peer support					
2	Focus groups (1 study), service evaluation forms (1 study)	People found it helpful to meet others in that they no longer felt alone and were able to exchange coping experiences and beneficial coping strategies. The presence of a peer counsellor increased the feeling of safety and fellowship and was valued as an important role model.	Limitations	Moderate concerns about methodological limitations[e]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[e]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [e]	
			Adequacy	No or very minor concerns about adequacy	
Group participation					
1	Service evaluation forms	Group participation was identified as an important part of the seminar delivery as it contributed to creating a collaborative and accepting atmosphere.	Limitations	Serious concerns about methodological limitations[g]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[g]	
			Adequacy	Moderate concerns about adequacy[g]	
Problems with the group setting					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Service evaluation forms	Issues raised included a lack of personal focus, difficulty in "opening up" in front of the group, feeling as if others were not as severely affected, information not being shared with the family, some attendees talking more than others and some negative comments made by other attendees.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Impact on friends, family and colleagues					
1	Semi structured interviews	The resources had an impact on the friends, family and colleagues. In some cases, the provision of evidence-based information improved relationships and strengthened support networks.	Limitations	Minor concerns about methodological limitations[h]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[h]	
			Adequacy	Moderate concerns about adequacy[h]	
Emotional impact					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Service evaluation forms	There were challenges inherent in confronting the reality of CFS/ME in the seminars; in particular information about prognosis was experienced as difficult.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Difficulty putting theory into practice					
1	Service evaluation forms	Some thought that applying the strategies into practice would be difficult as it depends on work, lifestyle and the severity of their CFS/ME.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[f]	
			Adequacy	Minor concerns about adequacy[f]	
Ongoing support					
2	Focus groups (1 study),	Several people wanted more guidance or follow-up to maintain the coping strategies after an education programme. Some mentioned	Limitations	Moderate concerns about methodological limitations[e]	LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	service evaluation forms (1 study)	that they were unsure about what happened next after the seminars.	Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[e]	PERM reanalysis: LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [e]	
			Adequacy	No or very minor concerns about adequacy	

[a]One study with serious methodological limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service) and one study with minor limitations due to unclear relationship between researcher and participants and no clear statement of findings (Bayliss 2016); minor concerns regarding relevance due to the lack of information on participant characteristics in one study (Bristol CFS/ME Service); PEM reanalysis: moderate concerns over relevance in both contributing studies due to the lack of information on participant characteristics including PEM in one study (Bristol CFS/ME Service) and participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM in the other study (Bayliss 2016).

[b]Two studies with minor methodological limitations due to no clear statement of findings in one study (Bayliss 2016), data analysis mainly by a single researcher in one study (Pinxsterhuis 2015) and an unclear relationship between researcher and participants in both studies (Bayliss 2016; Pinxsterhuis 2015) and one study with serious limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); minor concerns regarding relevance due to the lack of information on participant characteristics in one study (Bristol CFS/ME Service); PEM reanalysis: moderate concerns about relevance with moderate concerns across contributing studies due to the lack of information on participant characteristics including PEM (Bristol CFS/ME Service), participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM in one study (Bayliss 2016) and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (for Fukuda 1994) criteria where (Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria (Pinxsterhuis 2015)

[c]Two studies with minor methodological limitations due to no clear statement of findings in one study (Bayliss 2016), data analysis mainly by a single researcher in one study (Pinxsterhuis 2015) and an unclear relationship between researcher and participants in both studies (Bayliss 2016; Pinxsterhuis 2015); PEM reanalysis: moderate concerns over relevance in both contributing studies due to participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM (Bayliss 2016) and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria (Pinxsterhuis 2015)

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[d]*One study with minor methodological limitations due to unclear relationship between researcher and participants and data analysis mainly by one researcher (Pinxsterhuis 2015); minor concerns regarding adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study; PEM reanalysis: moderate concerns over relevance due to participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria in the contributing study (Pinxsterhuis 2015)*

[e]*One study with minor methodological limitations due to unclear relationship between researcher and participants and data analysis mainly by one researcher (Pinxsterhuis 2015) and one study with serious limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); minor concerns regarding relevance due to lack of information on participant characteristics reported in one study (Bristol CFS/ME Service); PEM reanalysis: moderate concerns regarding relevance in both studies, due to lack of information on participant characteristics including PEM in one study (Bristol CFS/ME Service) and participants having been diagnosed based on the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria where (for Fukuda 1994) PEM was not a compulsory feature and not being possible to distinguish how many participants had been diagnosed with each set of criteria (Pinxsterhuis 2015)*

[f]*One study with serious methodological limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); moderate concerns regarding relevance due to lack of information on participant characteristics in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study. PEM reanalysis: moderate concerns regarding relevance due to lack of information on participant characteristics including PEM (Bristol CFS/ME service)*

[g]*One study with serious methodological limitations due to no clear statement of research aim, recruitment strategy and participant characteristics not clearly described, unclear relationship between researchers and participant and unclear consideration of ethical issues (Bristol CFS/ME Service); moderate concerns regarding relevance due to lack of information on participant characteristics in the contributing study; moderate concerns about adequacy as the evidence is not sufficiently deep and only based on one study; PEM reanalysis: moderate concerns regarding relevance due to lack of information on participant characteristics including PEM (Bristol CFS/ME service)*

[h]*One study with minor limitations due to an unclear relationship between researcher and participants and no clear statement of findings (Bayliss 2016); moderate concerns about adequacy as the evidence is not sufficiently deep and only based on one study; PEM reanalysis: moderate concerns about relevance due to participants being selected by GPs after excluding other conditions but unclear if selection was also based on PEM (Bayliss 2016)*

Table 128: Summary of evidence: Rehabilitation/condition management programmes

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Accessibility					
1	Mixed methods (focus	Timing of the sessions in the afternoon and a venue which had a lift and high-backed chairs made the programme accessible.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	groups and questionnaire)		Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	
Accessibility					
1	Online survey	Travel required to access the clinic and carpark and waiting time were found to be less helpful/beneficial.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	
Validation					
1	Online survey	Obtaining a diagnosis and validation of symptoms was a key process.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Coherence	No or very minor concerns about coherence	(no change after PEM reanalysis)
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	
Lack of attendance pressure					
1	Mixed methods (focus groups and questionnaire)	There had been no pressure when people missed a week; they felt welcome and appreciated how encouraged they felt to return to the programme.	Limitations	Serious concerns about methodological limitations[c]	VERY LOW
			Coherence	Moderate concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance [c]	
			Adequacy	Moderate concerns about adequacy[c]	
Handouts					
1	Mixed methods (focus groups and questionnaire)	Having handouts was helpful, especially if they were given out at the beginning of the session as it saved energy used to take notes.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	
Video conferencing					
1	Mixed methods (focus groups and questionnaire)	It was suggested that incorporating video calls for example through Skype, Facetime or webcam would be useful for patients who were housebound at the time of the programme.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	
Duration					
1	Mixed methods (focus	There were mixed opinions on the duration of each session. Some felt that the sessions were too long and that 1.5 hours would be a more manageable duration than 2 hours.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	groups and questionnaire)		Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Self-management					
2	Mixed methods (focus groups and questionnaire) (1 study), online survey (1 study)	It was beneficial to learn about the use of diaries, boom and bust patterns, knowing limits, prioritising, planning ahead, time management and pacing, how to rest properly, diet, learning 'not to be so hard on yourself' and the practicalities and the help available to return to work. Additional topics people would like to be covered included benefits, the impact of sunny weather, pain management and stress recognition and management.	Limitations	Serious concerns about methodological limitations[d]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance [d]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[d]	
Signposting					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Online survey	Some referred to the signposting process as a beneficial aspect.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	
Science behind ME/CFS					
2	Mixed methods (focus groups and questionnaire) (1 study), online survey (1 study)	Some people appreciated learning the science behind ME/CFS, although some requested less medical content.	Limitations	Serious concerns about methodological limitations[e]	VERY LOW
			Coherence	Moderate concerns about coherence[e]	
			Relevance	Minor concerns about relevance[e]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[e]	
			Adequacy	Moderate concerns about adequacy[e]	
Relationships					
1	Mixed methods (focus	Some emphasised the value of discussing the impact of ME on relationships with people who understand.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	groups and questionnaire)		Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Exercise/physical activity					
1	Mixed methods (focus groups and questionnaire)	Views on physical activity advice were mixed.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[a]	VERY LOW (no change)
			Adequacy	Moderate concerns about adequacy[a]	
Group setting					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
2	Mixed methods (focus groups and questionnaire) (1 study), online survey (1 study)	People placed great value on meeting other patients and hearing others' stories, which helped create a support network. Those who had one-on-one sessions in addition to the group sessions also deemed this as helpful.	Limitations	Serious concerns about methodological limitations[f]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[f]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[f]	
			Adequacy	Moderate concerns about adequacy[f]	
Additional and ongoing support					
1	Mixed methods (focus groups and questionnaire)	People appreciated having follow-up at three and six months. Several would have liked one-off crisis-type access for during a deterioration or relapse and suggested that some people would require longer-term support.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Moderate concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	
Staffing					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Online survey	People found staff support, knowledge and individual approaches to be helpful/beneficial. People wanted nutritionist support and counselling services to be provided.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[b]	

[a]*One study with serious methodological limitations due to only those who completed the programme being recruited, unclear relationship between the interviewer and the participants, unclear consideration of ethical issues, data analysis by individual researcher, insufficient data presented to support all findings and no clear statement of some findings (Snounou); moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study; PEM reanalysis: moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study (Snounou)*

[b]*One study with serious methodological limitations due to recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants, unclear methods of data analysis and no clear statement of findings (Pemberton 2019); moderate concerns regarding relevance due to lack of information on participant characteristics including PEM in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study.*

[c]*One study with serious methodological limitations due to only those who completed the programme being recruited, unclear relationship between the interviewer and the participants, unclear consideration of ethical issues, data analysis by individual researcher, insufficient data presented to support all findings and no clear statement of some findings (Snounou); moderate concerns about the coherence of the finding with description of lack of pressure, but also anxiety about missing sessions in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study; PEM reanalysis: moderate concerns about relevance due to a lack of sufficient information on the population and unclear whether the ME/CFS diagnosis had been based on PEM in the contributing study (Snounou)*

[d]*Two studies with serious methodological limitations due to unclear consideration of ethical issues, data analysis by an individual researcher and insufficient data presented to support all findings in one study (Snounou), unclear methods of data analysis in one study (Pemberton 2019) and recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants and no clear statement of some findings in both studies (Snounou; Pemberton 2019); moderate concerns regarding adequacy, with no clear statement of the finding in either study; PEM reanalysis: moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies (Pemberton 2019; Snousnou)*

[e]*Two studies with serious methodological limitations due to unclear consideration of ethical issues, data analysis by an individual researcher and insufficient data presented to support all findings in one study (Snounou), unclear methods of data analysis in one study (Pemberton 2019) and recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants and no clear statement of some findings in both studies (Snounou; Pemberton 2019); moderate concerns about the coherence of the finding with one study suggesting that science was beneficial (Snounou) and the other suggesting that people wanted less medical content (Pemberton 2019);*

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minor concerns regarding relevance due to lack of information on participant characteristics in one study (Pemberton 2019); moderate concerns regarding adequacy, with no clear statement of the finding in either study; PEM reanalysis: moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies (Pemberton 2019; Snousnou)

[f]Two studies with serious methodological limitations due to unclear consideration of ethical issues, data analysis by an individual researcher and insufficient data presented to support all findings in one study (Snounou), unclear methods of data analysis in one study (Pemberton 2019) and recruitment potentially favouring those who completed treatment, unclear relationship between researchers and participants and no clear statement of some findings in both studies (Snounou; Pemberton 2019); minor concerns regarding relevance due to lack of information on participant characteristics in one study (Pemberton 2019); moderate concerns regarding adequacy, with no clear statement of the finding in either study; PEM reanalysis: moderate concerns about relevance due to lack of information on participant characteristics including PEM in both studies (Pemberton 2019; Snousnou)

Table 129: Summary of evidence: Complementary and alternative therapies

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Range of complementary and alternative therapies					
1	Mixture of structured and semi structured questions interviews	People desperate for relief of symptoms tried a wide range of different alternative therapies.	Limitations	Moderate concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance [a]	
			Adequacy	Minor concerns about adequacy[a]	
Holistic approach					
1	Mixture of structured and semi	People with ME/CFS were attracted to alternative therapies by a holistic approach.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	structured questions interviews		Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[b]	
Positive therapist approach					
1	Mixture of structured and semi structured questions interviews	Therapists' positive approaches gave people hope that it was possible to overcome the illness.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[b]	
Effectiveness					
2	Mixture of structured and semi	Evaluations of the effectiveness of alternative therapies were mixed. Some experienced temporary effectiveness which reinforced their beliefs in these therapies.	Limitations	Moderate concerns about methodological limitations[c]	VERY LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	structured questions interviews		Coherence	Moderate concerns about coherence[c]	
			Relevance	Moderate concerns about relevance[c]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [c]	
			Adequacy	Minor concerns about adequacy[c]	
Follow up					
1	Mixture of structured and semi structured questions interviews	Several people with ME/CFS were impressed that unlike their regular doctors, alternative therapists called periodically to find out how they were managing.	Limitations	Serious concerns about methodological limitations[b]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[b]	PEM reanalysis: VERY LOW (no change
			Relevance (PEM)	Serious concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[b]	

[a]One study with serious methodological limitations due to identification of HCPs by patients with ME/CFS, unclear relationship between participants and researcher, data analysis by a single researcher and no clear statement of findings (Beaulieu 2000) and nothing to lower our confidence in the other contributing study (de Carvalho Leite 2011); moderate concerns regarding relevance due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011); minor concerns about adequacy as there were no clear statements of findings in one study (Beaulieu 2000); PEM reanalysis: serious concerns regarding relevance with serious concerns in both contributing studies due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM in one study (Beaulieu 2000), lack of details on diagnosis (including PEM) of the purposive sample used in the other study (de Carvalho Leite 2011) and due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011)

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[b]*One study with serious methodological limitations due to identification of HCPs by patients with ME/CFS, unclear relationship between participants and researcher, data analysis by a single researcher and no clear statement of findings (Beaulieu 2000); moderate concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding and evidence only based on one study; PEM reanalysis: serious concerns regarding relevance due to different research aim and limited detail on interventions received in the contributing study and due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM (Beaulieu 2000).*

[c]*One study with serious methodological limitations due to identification of HCPs by patients with ME/CFS, unclear relationship between participants and researcher, data analysis by a single researcher and no clear statement of findings (Beaulieu 2000) and nothing to lower our confidence in the other contributing study (de Carvalho Leite 2011); moderate concerns regarding coherence as effectiveness was mixed in one study (Beaulieu 2000), but alternative therapies were reported to be helpful overall in the other study (de Carvalho Leite 2011); moderate concerns regarding relevance due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011); minor concerns about adequacy as there were no clear statements of findings in one study (Beaulieu 2000); PEM reanalysis: serious concerns regarding relevance in the contributing studies due to the diagnosis being made by a medical doctor but it being unclear if it had also been based on PEM in one study (Beaulieu 2000), lack of details on diagnosis (including PEM) of the purposive sample used in the other study (de Carvalho Leite 2011) and due to different research aims and limited detail on interventions received in both studies (Beaulieu 2000; de Carvalho Leite 2011)*

Table 130: Summary of evidence: Pharmacological interventions

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Antidepressants					
1	Survey including open ended questions	Antidepressants were prescribed for ME symptoms by health care professionals, and people experienced negative side effects.	Limitations	Serious concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			PEM Relevance	Moderate concerns about relevance [b]	
			Adequacy	Moderate concerns about adequacy[a]	

[a]*One study with serious methodological limitations due to recruitment through a single ME/CFS charity, unclear detail on specific interventions received, unclear consideration of ethical issues, limited detail reported on methods of data analysis and no clear statement for all findings (Leary 2019); moderate concerns regarding relevance due to lack of*

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information on participant characteristics in the contributing study; moderate concerns regarding adequacy, with no clear statement of the finding with elaboration and examples and evidence only based on one study.

[b] Moderate concerns regarding relevance due to lack of information on participant characteristics including PEM which was self-reported in the contributing study.

Children/young people (severity mixed/unclear)

Table 131: Summary of evidence: Cognitive behavioural therapy

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Relationship with the therapist					
1	Semi structured interviews	The therapist's personality and interpersonal skills were important. Having somebody to talk to who was interested in and understood CFS was a key positive feature of therapy sessions.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Acceptability of FITNET-NHS platform/ e-consultations					
1	Semi structured interviews	People liked that they could complete the platform in their own time and think about their answers. Some found it easier to talk about personal topics over email, whereas others found it difficult	Limitations	No or very minor concerns about methodological limitations	MODERATE

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
		to portray things in writing and would have preferred some face to face contact.	Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: LOW
			Relevance (PEM)	Moderate concerns about relevance[b]	
			Adequacy	Minor concerns about adequacy[b]	
Validation					
1	Semi structured interviews	Recognition, validation and emotional support were almost always cited as important and benefits were appreciated regardless of whether other aspects of the therapy were deemed useful.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Behavioural aspects					
1		The behavioural aspects of the therapy were particularly valued and accepted by the young people, although many struggled	Limitations	No or very minor concerns about	LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
	Semi structured interviews	putting them in to practice. Tasks were often initially very hard to achieve and parents found it challenging to watch their children push themselves.		methodological limitations	
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Personalised care					
2	Semi structured interviews	Some parents felt the agenda during the sessions was too narrow and rigid and therefore unresponsive to families' idiosyncratic issues. Participants valued the individual tailored advice from a specialist CFS/ME therapist.	Limitations	No or very minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance[c]	PEM reanalysis: LOW
			Relevance (PEM)	Serious concerns about relevance[c]	
			Adequacy	No or very minor concerns about adequacy	
Inclusion of the family					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Sessions functioned as support for parents and young people felt they needed their parent/s at the sessions for emotional support. Despite this, many felt that there were certain situations and issues where the young person should have been seen alone.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Psychological aspects					
1	Semi structured interviews	Several disliked the 'psychological' or 'emotional' aspects, finding them irrelevant or inappropriate. Some felt pigeonholed and subjected to generalisations.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Effectiveness					
1	Semi structured interviews	The therapy was useful to some extent, the family was thankful for the help, but improvements were modest. However, the therapy was a principle factor in regaining normality and viewed as a 'starting block' on a gradual journey to recovery.	Limitations	No or very minor concerns about methodological limitations	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Effectiveness					
1	Semi structured interviews	Some young people with ME/CFS and depression found CBT helpful and the combination treatment of CBT and medication was also discussed.	Limitations	Minor concerns about methodological limitations[d]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[d]	PEM reanalysis: VERY LOW
			Relevance (PEM)	Serious concerns about relevance[d]	
			Adequacy	Minor concerns about adequacy[d]	

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[a]*Moderate concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study (Dennison 2010); minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study; PEM reanalysis: serious concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in the contributing study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis (Dennison 2010).*
[b]*Minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study (Anderson);* PEM reanalysis: m*oderate concerns regarding relevance as participants fulfilled criteria where PEM was not compulsory (Anderson).*
[c]*Minor concerns regarding relevance due to findings for both CBT and psychoeducation interventions being combined in one study (Dennison 2010), but no concerns in the other study (Anderson);* PEM reanalysis: *serious concerns regarding relevance with serious concerns in one study due to findings for both CBT and psychoeducation interventions being combined in one study and participants fulfilling criteria that did not include PEM or where PEM was not compulsory for diagnosis (Dennison 2010), and moderate concerns in the other study as participants fulfilled criteria where PEM was not compulsory (Anderson). .*
[d]*One study with minor methodological limitations due to insufficient data presented to support all findings, with some supported by single quotes and no clear statement of all findings (Taylor 2017); moderate concerns regarding relevance due to the study population having comorbid depression in the contributing study; minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study; PEM reanalysis: serious concerns regarding relevance due to the study population having comorbid depression and no details available on PEM (Taylor 2017).*

Table 132: Summary of evidence: The Lightning process

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Relationship with the therapist					
1	Semi structured interviews	Therapists and staff were mostly described as positive and encouraging. There were different opinions about the therapists; some had only good experiences, while others found their therapist too controlling and not open for critical questions. Alternative viewpoints brought up by the young people were not well-received and a few experienced pressure to be happy all the time and not express any negative feelings. Those who did not recover felt that they were blamed for the lack of treatment success and consequently struggled with feelings of guilt and anger.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Dishonesty					
1	Semi structured interviews	People criticised the impression that staff gave about the Lightning Process always involving a quick recovery and the dishonesty staff showed when they claimed the treatment had a 100% success rate.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Theory behind the Lightning Process					
1	Semi structured interviews	The educational part of the treatment, including the theory behind the Lightning Process and practical examples of previous success stories, gave people a rationale they could believe in.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy[a]	
Confusing					
1	Semi structured interviews	The educational part of the intervention was considered as complicated and difficult to understand, but necessary and helpful. Some found the teaching incomplete and not well-organised. Advice that participants could do anything they wanted conflicted with previous advice they had been given around activity pacing.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Peer support					
1	Semi structured interviews	The support from others and the group setting that allowed people to learn from each other was highlighted as helpful aspects leading to engagement and treatment commitment.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Goal setting					
1	Semi structured interviews	The focus on specific goals and identifying barriers from reaching them was considered a helpful part of treatment.	Limitations	Moderate concerns about methodological limitations[b]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Moderate concerns about adequacy[b]	
Practice and application					
1	Semi structured interviews	The practical assignments were described as important for rapid recovery. People realised that it was their own choice that would really help them recover and the behavioural aspects of the treatment stood out as the most important factor for symptom alleviation and continuing recovery.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Intensity					
1	Semi structured interviews	The length of the sessions was thought to be too long and intense, especially since many participants struggled with focus and concentration.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	
Follow up					
1	Semi structured interviews	Some described the whole treatment as too short; with too little follow up afterwards.	Limitations	Moderate concerns about methodological limitations[b]	LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Moderate concerns about adequacy[b]	
Effectiveness					
1	Semi structured interviews	Some experienced an instant healing, some experienced a gradual improvement that continued after treatment ended and some did not find the treatment helpful.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis:
			Relevance (PEM)	Moderate concerns about relevance[c]	VERY LOW
			Adequacy	Minor concerns about adequacy[a]	
Secrecy					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	The secrecy surrounding the Lightning Process was criticised and thought to result in unnecessary sceptical and prejudiced attitudes from people. Participants were specifically encouraged not to talk to anyone about it and they found this unhelpful and difficult.	Limitations	Moderate concerns about methodological limitations[a]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	PEM reanalysis: VERY LOW
			Relevance (PEM)	Moderate concerns about relevance[c]	
			Adequacy	Minor concerns about adequacy[a]	

[a]*One study with moderate methodological limitations due to recruitment through a single charity and insufficient data presented to support all findings (Reme 2013); minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study.*
[b]*One study with moderate methodological limitations due to recruitment through a single charity and insufficient data presented to support all findings (Reme 2013); moderate concerns about adequacy as the evidence is not sufficiently deep and only based on one study.*
[c] moderate concerns about relevance due the majority of participants meeting Sharpe 1991 criteria (Oxford criteria) where PEM was not a compulsory feature for diagnosis and no further details on PEM or any additional criteria met.

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Table 133: Summary of evidence: The Lightning process (mild/moderate severity)

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Validation					
1	Semi structured interviews	The service recognised and acknowledged the young person's condition, resulting in a sense of relief and reassurance that symptoms were now being understood and they would receive help.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Personalised care					
1	Semi structured interviews	Families had access to an informative team of experts, for some a formal diagnosis, and for all a tailored, patient centred specialist medical intervention that had not been available earlier. This enabled positive change and steps towards a managed recovery.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Professional support					
1	Semi structured interviews	Some found specialist medical care to be positive, as it enabled them to talk about their illness and gave guidance on how to	Limitations	Minor concerns about methodological limitations[a]	LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
		manage their condition, which brought structure and a sense of normality back into their lives.	Coherence	No or very minor concerns about coherence	(PEM reanalysis: no change)
			Relevance	Moderate concerns about relevance[a]	
			Adequacy	Minor concerns about adequacy[a]	
Challenges of a new routine					
1	Semi structured interviews	Some people reported that, although specialist medical care resulted in better symptom management, accepting that for a time they must reduce activity levels and adopt a routine was challenging. Mothers also noted that specialist medical care strategies had an impact on the whole family and could be difficult to integrate with their lifestyle.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance	
			Adequacy	Minor concerns about adequacy[a]	
Dialogue between healthcare professionals and education providers					
1	Semi structured interviews	The service opened channels of dialogue between health-care professionals and education providers.	Limitations	Minor concerns about methodological limitations[a]	LOW (PEM reanalysis: no change)
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
			Adequacy	Minor concerns about adequacy[a]	

[a]*One study with minor methodological limitations due to an unclear relationship between the researcher and participants and some findings supported by single quotes only (Beasant 2014); moderate concerns regarding relevance as the contributing study aimed to understand the experiences of accessing as well as using a specialist service and some participants had not yet used the service and it was unclear which intervention the findings relate to; minor concerns about adequacy as the evidence is sufficiently deep, with elaboration and examples, but only based on one study.*

Table 134: Summary of evidence: Graded exercise therapy/other exercise interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Exercise enjoyable					
1	Semi structured interviews	Despite mixed preconceptions, most participants were positive about GET once they entered treatment and reported positive experience of the exercises.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy[a]	

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Routine and structure					
1	Semi structured interviews	Many families explained that the program introduced routine, which they experienced as important.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Relationship with therapist					
1	Semi structured interviews	Many families valued the support they received from their clinician in terms of having someone listen and understand and feeling cared for.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Personalised care					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Families praised the way the program was tailored so that the clinician identified the individual needs of the young person and collaboratively developed a tailored treatment plan, recognising the fluctuating nature of CFS/ME and that physical capabilities change. Families also reported that they gained extra advice beyond the central focus on activity, such as sleep or diet, when these came up for participants.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Pacing benefits					
1	Semi structured interviews	Some commented that the treatment set helpful boundaries to avoid a pattern of overexertion and that clinicians were flexible in reducing the activity if the increase had been too rapid/ too much.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Pacing challenges					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Some found limiting activity was challenging, with evidence that the young person resisted this advice, wanting to do more physical exercise. Concerns about activity reduction included social effects and difficulties with limiting walking in school.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Setbacks					
1	Semi structured interviews	Families described that the young person had a setback or “crash” during the course of treatment, as a result of exceeding the recommended limits of physical activity. Travel to the hospital site for appointments contributed to setbacks.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
FITBITS and physical monitoring					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Participants commented positively on the use of wearables to accurately detect physical activity, as this demonstrated when they were doing too much and provided other useful functionality such as sleep or steps monitoring in addition to heart rate monitoring. Some comments indicated that the measurements were not always accurate.	Limitations	No or very minor concerns about methodological limitations	MODERATE (no change after PEM reanalysis)
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[b]	
Positive outcomes					
1	Semi structured interviews	There was overall recognition that the young people had benefitted from GET, including reductions in fatigue and tiredness, improved sleep, ability to concentrate, functioning and mood.	Limitations	No or very minor concerns about methodological limitations	LOW (no change after PEM reanalysis)
			Coherence	Moderate concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[c]	
Uncertain/lack of difference from treatment					
1			Limitations	No or very minor concerns about	LOW

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	Semi structured interviews	Some families did not notice a difference with treatment, either reporting uncertainty, or lack of impact, often related to school and cognitive activities.		methodological limitations	(no change after PEM reanalysis)
			Coherence	Moderate concerns about coherence[c]	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy[c]	

[a]*Moderate concerns regarding adequacy due to there being no elaboration or examples of positive experiences and the finding only being based on one study (Brigden (Beasant)).*
[b]*Minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study (Brigden (Beasant)).*
[c]*Moderate concerns regarding coherence as the finding conflicts with another finding from the same study (Brigden (Beasant)); minor concerns about adequacy as the evidence is sufficiently deep, with a clear statement of the finding with elaboration and examples, but only based on one study.*

Table 135: Summary of evidence: Complementary and alternative therapies

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Alternative therapies					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
1	Semi structured interviews	Some families sought treatments such as acupuncture, dietician input, sickness bands and the emotional freedom technique, while others spoke to their CFS/ME clinician for advice. External support varied greatly in perceived accessibility and helpfulness.	Limitations	Moderate concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[a]	
			Adequacy	Moderate concerns about adequacy[a]	

[a]*One study with moderate methodological limitations due to involvement of clinicians in determining participant eligibility that may have introduced selection bias and lack of data richness (Harris 2017); moderate concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties in the contributing study; moderate concerns regarding adequacy, with no elaboration or examples and evidence only based on one study; PEM reanalysis: serious concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties in the contributing study and it being unclear whether diagnosis had been based on PEM.*

Table 136: Summary of evidence: Pharmacological interventions

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Sickness/stomach acid relief medication					

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Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	**Design**		**Criteria**	**Rating**	**Overall assessment of confidence**
1	Semi structured interviews	Some took prescribed sickness or stomach acid relief medication which they found helpful. However, it was not common to have been offered medication to relieve their symptoms which frustrated some people.	Limitations	Moderate concerns about methodological limitations[a]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[a]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[b]	
			Adequacy	Moderate concerns about adequacy[a]	
Attitude toward medication					
1	Semi structured interviews	Young people generally did not mind taking medication providing they found it helpful.	Limitations	Minor concerns about methodological limitations[c]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[c]	PEM reanalysis: VERY LOW (no change)
			Relevance (PEM)	Serious concerns about relevance[d]	
			Adequacy	Moderate concerns about adequacy[c]	

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[a]One study with moderate methodological limitations due to involvement of clinicians in determining participant eligibility that may have introduced selection bias and lack of data richness (Harris 2017); moderate concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties in the contributing study; moderate concerns regarding adequacy, with no elaboration or examples and evidence only based on one study.

[b] Serious concerns regarding relevance due to the population being limited to adolescents with ME/CFS who experienced eating difficulties and it being unclear if participants had PEM (Harris 2017)

[c]One study with minor methodological limitations due to insufficient data presented to support all findings and no clear statement of all findings (Taylor 2017); moderate concerns about relevance due to the study population having comorbid depression/ PEM reanalysis: serious concerns about relevance due to the study population having comorbid depression and it being unclear if participants had PEM; moderate concerns regarding adequacy, with no elaboration or examples and only based on one study.

[d] Serious concerns about relevance due to the study population having comorbid depression and it being unclear if participants had PEM (Taylor 2017)

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Appendix F PEM reanalysis

F.1 PEM reanalysis – Methods and rationale

After considering the stakeholder comments about the inclusion of PEM in the diagnostic criteria of ME/CFS being applied differently across the quantitative and the qualitative evidence, the committee agreed to revisit the evidence for the intervention reviews further scrutinising the information on PEM reported in the studies and its impact on concerns over applicability at the individual study level and in turn, on the relevance rating given to the findings that the studies contributed to. The committee agreed the requirement of PEM was particularly important in the studies evaluating interventions as they considered that the response to an intervention is likely to be different in people who have PEM compared to those who do not, and this should be taken into account when interpreting the evidence.

We looked for any published information on the percentage of participants with PEM in the included studies, or subgroup analyses in study participants with PEM. The papers for all included studies were reviewed again, as well as any published supplementary papers that could include relevant information about the populations of the included studies, which were identified from the included studies or the references in the included studies. The excluded studies list was also re-examined to ensure any relevant information relating to PEM in the included studies was not missed. Unpublished data was not accepted for this analysis.

The committee agreed that studies using criteria without PEM as a compulsory feature (e.g. 1994 CDC criteria, Oxford criteria) should not be downgraded if a high proportion of study participants had PEM and this was adequately described. In order to not downgrade, the following criteria must be met:

- ≥95% of study participants are reported to have PEM (or a subgroup analysis where ≥95% participants are reported to have PEM)

AND

- If another term is used other than PEM (e.g. post-exertional fatigue) there must be a clear description that indicates all of the following:
    - Symptom worsening that follows minimal physical or mental activity that was previously tolerated
    - Symptom worsening is typically delayed (12-24 hours after the activity)
    - The impact is prolonged

OR

- ≥95% of study participants meet a diagnostic criteria where PEM is compulsory (e.g. IOM 2015, NICE 2007, Carruthers 2003/Canadian criteria).

The committee also noted that for these criteria to be met, PEM needed to have been assessed by a clinician based on the aforementioned diagnostic criteria and not to have been self-reported by the participants included in the studies. Before reviewing the results of the PEM reanalysis, the committee agreed it was appropriate that studies not meeting the PEM criteria are downgraded for moderate concerns over applicability if there were no additional concerns impacting applicability. Downgrading further to serious concerns was appropriate where in addition to not meeting criteria for PEM, there were further concerns not relating to PEM to further lower our confidence.

Information gathered through the PEM reanalysis and its impact on concerns over applicability of the studies are reported below. These, are also incorporated in the Qualitative evidence tables in Appendix D for the Experiences of interventions section in the current

review and in section 2.1.4 in the Summary of qualitative studies included in the Evidence review G. The impact of this on the relevance rating and the overall assessment of confidence in each review finding has been added throughout the relevant sections of Evidence report G (in section 2.1.5 in the Narrative summary of the review findings and in section 2.1.6 in the Qualitative evidence summary tables), and in Appendix E: Qualitative evidence summary in Evidence report H alongside the original results. The committee's discussion of the evidence can be found in Evidence review G section 3.

F.2 PEM reanalysis – Reporting of PEM

Summary of PEM reporting in each study

Study	Intervention	Reporting of PEM	Effect on applicability
Bayliss 2016[58]	Education/information interventions (Resources for practitioners and patients to support the diagnosis and management of 'CFS/ME' in primary care)	The percentage of participants with PEM was not reported.	Downgraded for moderate concerns due to participants being selected by GPs after excluding other conditions but it being unclear if selection was also based on PEM.
Beasant 2014[65]	Specialist medical care + Lightning Process	Diagnosis based on NICE 2007 criteria where PEM is compulsory feature	Not downgraded for PEM but remain downgraded for other existing concerns.
Beaulieu 2000[66]	Complementary and alternative therapies	The percentage of participants with PEM was not reported.	Further downgraded for serious concerns due to limited details on the interventions received and percentage of participants with PEM unclear.
Broadbent 2020[92]	Aquatic exercise intervention	The percentage of participants with PEM was not reported; diagnosis was based on the International Canadian Consensus criteria or the 1994 Fukuda criteria	Further downgraded for serious concerns due to existing reasons and it being unclear if participants had PEM as it is not a compulsory feature in the 1994 Fukuda criteria and the number of those diagnosed using the International Canadian Consensus criteria cannot be determined.
Cheshire 2020[154]	Guided graded Exercise Self-help	Diagnosis based on NICE 2007 criteria where PEM is compulsory feature	Remains not downgraded
Dennison 2010[231]	Family focused CBT	PEM not reported; original RCT	Further downgraded from moderate

Study	Intervention	Reporting of PEM	Effect on applicability
	Psychoeducation	participants had to meet the Oxford or the 1994 CDC criteria (Fukuda) for diagnosis	concerns (due to other reasons) to serious concerns due to PEM unclear.
Harris 2017[313]	General	The percentage of participants with PEM was not reported.	Further downgraded from moderate concerns (due to other reasons) to serious concerns due to PEM unclear.
Larun 2011[430]	Comprehensive treatment program for CFS patients including physical activities in addition to physiotherapy, theme discussions and individual counselling	The percentage of participants with PEM was not reported.	Further downgraded from moderate concerns (due to other reasons) to serious concerns due to PEM unclear.
Picariello 2017[589]	Face-to-face CBT	The percentage of participants with PEM was not reported; diagnosis in original RCT based on participants meeting both the CDC (Fukuda) and oxford (Sharpe 1991) criteria	Downgraded for moderate concerns due to participants meeting criteria where PEM was not compulsory
Pinxsterhuis 2015[592]	Patient education program	The percentage of participants with PEM was not reported; participants meeting the Canadian diagnostic criteria (Carruthers 2003) and/or the Centres of Disease Control and Prevention (Fukuda 1994) criteria	Downgraded for moderate concerns with PEM being a compulsory feature in only one set of criteria used to exclude participants (Canadian) and not the other (CDC 1994) and not possible to distinguish how many were included based on each set of criteria.
Reme 2013[621]	Lightning Process	The percentage of participants with PEM was not reported; 8/9 participants met Sharpe 1991 criteria (i.e. Oxford criteria)	Downgraded for moderate concerns due to participants meeting criteria where PEM was not compulsory
Taylor 2017[728]	General	The percentage of participants with PEM was not reported	Further downgraded for serious concerns due to existing reasons and unclear PEM.

Study	Intervention	Reporting of PEM	Effect on applicability
Ward 2008[826]	Any type of counselling intervention delivered by a counsellor, therapist, or clinical psychologist	The percentage of participants with PEM was not reported	Further downgraded for serious concerns due to existing reasons and unclear PEM.
Studies identified through the call for evidence			
Anderson[22]	Online CBT (FITNET-NHS)	The percentage of participants with PEM was not reported; FITNET trial recruitment was based on the Fukuda criteria where PEM is not compulsory	Downgraded for moderate concerns due to unclear PEM
Brigden[88] **(Beasant[64])**	Graded exercise therapy; activity management	The percentage of participants with PEM was not reported but participants (originally recruited in the MAGENTA RCT) met the NICE criteria where PEM is compulsory	Not downgraded
Bristol CFS/ME service[90]	'CFS/ME' seminars	The percentage of participants with PEM was not reported.	Remain downgraded for moderate concerns (percentage of participants with PEM unclear)
Bristol CFS/ME service[540]	General	The percentage of participants with PEM was not reported.	Remain downgraded for moderate concerns (percentage of participants with PEM unclear)
De Carvalho Leite 2011[220]	General	The percentage of participants with PEM was not reported.	Further downgraded for serious concerns due to existing reasons and percentage of participants with PEM unclear.
Forward ME survey 2019[564]	CBT GET CBT + GET combined	The percentage of participants with PEM was not reported; diagnostic criteria used where unclear; percentage of PEM was self-reported.	Downgraded for moderate concerns as the experience of PEM was self-reported
Gladwell 2014[291]	Graded exercise therapy (GET), the functionally oriented	The percentage of participants with PEM was not reported.	Downgraded for moderate concerns

Study	Intervention	Reporting of PEM	Effect on applicability
	Graded Activity Therapy (GAT), or Exercise on Prescription (EOP)		(percentage with PEM unclear)
McManimen 2019[497]	General	The percentage of participants with PEM was self-reported; diagnostic criteria used were unclear	Further downgraded for serious concerns due to existing reason and percentage of participants with PEM being self-reported and therefore unclear
ME Action 2019[435]	General	The percentage of participants with PEM was self-reported; diagnostic criteria used were unclear	Not downgraded further (moderate concerns due to lack of information on participant characteristics and PEM being self-reported).
Physios for ME[583]	Physiotherapy	The percentage of participants with PEM was not reported; diagnostic criteria used were unclear	Further downgraded for serious concerns due to existing reasons and unclear PEM
Snounou 2019[690]	Eight-week group condition management programme	The percentage of participants with PEM was not reported; diagnostic criteria used were unclear	Downgraded for moderate concerns due to unclear PEM
Yorkshire Fatigue clinic[581]	Tailored rehabilitation programme	The percentage of participants with PEM was not reported; diagnostic criteria used were unclear	Not downgraded further (moderate concerns due to lack of information on participant characteristics and PEM being self-reported).

Appendix G Excluded studies

Reference	Reason for exclusion
Aikman 1995[13]	Unable to obtain paper (thesis)
Ali 2019[17]	No relevant themes
Alameda Cuesta 2019[15]	Incorrect population (ME/CFS, fibromyalgia and multiple chemical sensitivity)
Anderson 1997[23]	Mixed method study design with no extractable themes
Anderson 2012[25]	Systematic review with different PICO

Reference	Reason for exclusion
Anderson 2014[24]	No relevant themes (brief discussion of alternative treatments, but no detail on experiences of specific interventions)
Antcliff 2016[30]	Incorrect population (Chronic low back pain, widespread pain, fibromyalgia and ME/CFS)
Arrol 2008[36]	No relevant themes
Asbring 2001[37]	Incorrect population (majority of population fibromyalgia)
Asbring 2004[38]	Incorrect population (ME/CFS and fibromyalgia)
Asbring 2002[39]	Incorrect population (CFS/fibromyalgia)
Ashby 2006[41]	No relevant themes
Ax 1997[46]	No relevant themes (brief discussion of complementary and alternative treatment, but no detail on experiences of specific interventions)
Ax 1998[45]	No relevant themes
Ax 2002[44]	No relevant themes
Bayliss 2014[59]	No relevant themes
Bayliss 2014[57]	Systematic review with different PICO
Bazelmans 2004[61]	Incorrect study design (quantitative questionnaire)
Bazelmans 2005[60]	Incorrect study design (quantitative analysis); Incorrect population (fatigued employees receiving CBT for fatigue)
Bennett 2007[70]	No relevant themes
Brady 2016[83]	Partially incorrect population (CFS and diabetes)
Brigden 2018[84]	No relevant themes
Brooks 2013[96]	No relevant themes; included interviews but findings based on incorrect study design (cross-sectional/questionnaire data)
Broughton 2017[98]	No relevant themes
Bulow 2003[110]	Incorrect population (CFS or related diagnosis in which unexplained fatigue makes up a significant part)
Caplan 2001[118]	Story
Catchpole 2019[127]	No relevant themes
Chernow 2008[153]	Unable to obtain paper (thesis)
Chew-Graham 2011[155]	No relevant themes
Chew-Graham 2010[156]	Incorrect population (GPs)
Chew-Graham 2008[157]	No relevant themes
Clarke 1999[165]	No relevant themes
Clarke 2000[166]	No relevant themes
Clements 1997[170]	No relevant themes
Costello 1998[190]	Unable to obtain paper (thesis)
Davison 1997[216]	No relevant themes
De Silva 2013[222]	Secondary analysis of Hannon 2012
Devendorf 2019[233]	Incorrect population (physicians)
Devendorf 2017[234]	Incorrect population (physicians)
Devendorf 2018[235]	No relevant themes
Donalek 2009[238]	No relevant themes
Drachler 2009[242]	Systematic review with different PICO
Edwards 2007[247]	No relevant themes (brief discussion of alternative treatments but no detail on experiences of specific interventions)
Everett 2002[253]	Incorrect population (teachers of people with ME/CFS); no relevant themes

Reference	Reason for exclusion
Fisher 2013[260]	No relevant themes
Fowler 2005[267]	Incorrect study design (quantitative analysis, no themes)
Friedberg 1998[271]	Book chapter
Friedberg 2016[270]	Incorrect population (majority 'unexplained chronic fatigue'); emphasis on quantitative analysis; no relevant themes
Gan 2010[277]	Incorrect population
Geraghty 2019[279]	Incorrect study design (quantitative survey)
Gilje 2008[290]	No relevant themes
Gotts 2016[296]	No relevant themes
Gray 2003[297]	No relevant themes
Guise 2010[300]	No relevant themes
Guise 2007[301]	No relevant themes
Haig-Ferguson 2019[304]	No relevant themes
Hannon 2012[308]	No relevant themes
Hareide 2011[310]	No relevant themes
Harland 2019[311]	No relevant themes
Harris 2016[312]	Systematic review with different PICO
Hart 2000[314]	No relevant themes
Higginson 2008[325]	Incorrect population (people who had experienced personal change and recovery following a significant problem)
Horrocks 2015[332]	Book chapter
Horton 2010[335]	Incorrect population (HCPs)
Horton-Salway 2002[333]	Incorrect study design (examination of case narratives/ unstructured interviews, no thematic or grounded theory analysis); incorrect population (GPs)
Horton-Salway 2004[334]	Article; incorrect analysis: discursive analysis of ME support group meeting
Jason 2015[360]	Article
Jelbert 2010[366]	No relevant themes
Jensen 2001[369]	Unable to obtain paper (thesis)
Keech 2015[380]	No relevant themes; qualitative data used to devise self-reported instrument for fatigue
Kendrick 2016[383]	Incorrect study design (quantitative survey analysis)
Kisely 2002[407]	Incorrect study design: evaluation of web-based information
Lacerda 2019[423]	No relevant themes
Landmark 2016[425]	Article not in English
Larun 2007[431]	Systematic review: references checked
Lee 2000[437]	Unable to obtain paper (thesis)
Lee 2001[438]	No relevant themes
Levine 1997[441]	Incorrect study design (no qualitative analysis)
Lian 2016[446]	No relevant themes
Lin 2009[449]	No relevant themes
Lingard 2014[451]	No relevant themes
Littrell 2012[452]	Unable to obtain paper (thesis)
Lombaard 2005[464]	No relevant themes
Lovell 1999[466]	No relevant themes
Marks 2016[477]	Incorrect population (HCPs)

Reference	Reason for exclusion
McCue 2004[490]	No relevant themes
McDermott 2011[491]	No relevant themes
McInnis 2015[495]	Majority population incorrect (unexplained illness)
Mengshoel 2020[507]	Systematic review: references checked
Mihelicova 2016[508]	Incorrect study design (secondary analysis)
Missen 2012[512]	No relevant themes
Moore 2000[516]	Incorrect population (occupational therapists)
Njolstad 2019[546]	No relevant themes
Olson 2015[560]	No relevant themes
Ong 2005[561]	Incorrect study design (qualitative case study)
Parslow 2017[571]	Systematic review: references checked
Parslow 2017[572]	Incorrect population (HCPs)
Parslow 2015[569]	No relevant themes
Parslow 2018[570]	No relevant themes
Pemberton 2014[579]	No relevant themes
Pemberton 2014[580]	No relevant themes
Pinikahana 2002[590]	No relevant themes
Pinxsterhuis 2015[593]	Systematic review: references checked
Prins 2000[607]	Mixed methods study design and qualitative analysis based on incorrect population (GPs)
Raine 2004[613]	Incorrect population (GPs)
Ray 1995[618]	Incorrect study design (quantitative analysis of questionnaire data)
Ray 1998[617]	No relevant themes
Reynolds 2010[622]	No relevant themes
Reynolds 2008[624]	No relevant themes
Reynolds 2006[623]	Incorrect study design (case series)
Richards 1998[627]	No relevant themes
Richards 2006[626]	Incorrect study design: questionnaires, no qualitative analysis; not extractable themes
Rowe 2020[647]	Incorrect study design (questionnaire with closed and open ended questions; no thematic analysis)
Ryckeghem 2017[653]	No relevant themes
Sachs 2001[655]	No thematic analysis
Saltzstein 1998[656]	No relevant themes
Schoofs 2004[667]	Incorrect population (CFS or FMS)
Sidi-Ali-Mebarek 2009[683]	Unable to obtain paper (thesis)
Snell 2001[689]	Incorrect study design: qualitative case study
Soderlund 2000[693]	No relevant themes
Soderlund 2005[692]	No relevant themes
Son 2015[695]	No relevant themes
Stenhoff 2015[700]	Incorrect population (medical students)
Stormorken 2015[707]	No relevant themes
Strassheim 2019[709]	Incorrect population (chronic fatigue; only 10/33 had ME/CFS)
Sturge-Jacobs 2002[717]	Incorrect population (fibromyalgia)
Sunnquist 2017[721]	Incorrect study design: quantitative (survey)

Reference	Reason for exclusion
Swoboda 2006[727]	Incorrect population (CFS/multiple chemical sensitivities/Gulf war syndrome)
Taylor 2005[731]	No relevant themes
Tevens 2004[739]	Unable to obtain paper (thesis)
Theorell 1999[757]	Incorrect study design (quantitative questionnaire)
Travers 2008[765]	No relevant themes
Tuck 2000[767]	No relevant themes
Tuck 1998[766]	Incorrect study design (quantitative questionnaire)
Van der Vaart 2019[784]	Incorrect population (therapists and managers)
Velleman 2016[792]	Incorrect population (siblings)
Ware 1998[828]	No relevant themes
Ware 1999[829]	No relevant themes
Ware 1993[827]	No relevant themes
Webb 2011[840]	No relevant themes
Whitehead 2006[850]	No relevant themes
Whitehead 2006[852]	No relevant themes
Wilde 2020[858]	No relevant themes
Williams 2016[859]	No relevant themes
Wilson 2011[865]	No relevant themes
Winger 2014[867]	No relevant themes
Woodward 1995[869]	No relevant themes

A call for evidence was sent out for three review questions for which the committee anticipated that there would be limited published evidence. Some articles were submitted with a clear indication of which of the three review questions they related to, but for many there was no clear indication. Regardless, all articles were assessed for eligibility for inclusion in all three reviews and one main table was created for all studies/articles submitted that were subsequently excluded. For some articles, there were multiple reasons for exclusion across the three review questions. The exclusion reason listed is the main reason for exclusion from the review that the article was judged to be most relevant to. For example, a quantitative study on the effectiveness of an intervention in people diagnosed with ME/CFS was considered to be most relevant to the experiences of interventions question, but the review protocol specified only qualitative studies to be included, so the main reason for exclusion would be incorrect study design. Some articles were relevant to the guideline in general, but did not specifically attempt to answer any of the three review questions.

Table 137: Studies excluded from the call for evidence

Study	Exclusion reason
Action for ME 2001[2]	Incorrect study design (quantitative survey)
Action for ME 2014[574]	No relevant themes
Action for ME 2019 Results from our big survey[1] (unpublished)	Incorrect study design (quantitative survey)
Action for ME and Association of Young People with ME (UK) 2008[3]	Incorrect study design (qualitative survey)
Adamowicz 2014[5]	Systematic review with different PICO
Adamson[8] (unpublished)	Incorrect study design (cohort)
Adedeji 2012[10]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Adelakun[11]	No useable data - qualitative data reported as most frequently occurring words
Ahmed 2020[12]	Incorrect study design (systematic review; no qualitative data)
All-Party Parliamentary Group on ME 2010[18]	Not a qualitative study
Allwright 2019[19]	No relevant themes
Anderson 1997[23]	Mixed method study design with no extractable themes
Anon[724]	Incorrect study design (quantitative survey)
Anon[669]	Incorrect study design (non-comparative intervention study)
Anon[28]	Incorrect study design (non-comparative intervention study with quantitative outcomes)
Anon 2013[575] (unpublished)	Incorrect study design (quantitative survey)
Anon 2015[172]	Trial registry record; no results posted
Anon 2015[670]	Incorrect study design (quantitative)
Anon 2015[29]	Unable to obtain
Anon 2016[56] (unpublished)	Letter/commentary/expert opinion
Anon 2016[619]	Study/article does not address any of the call for evidence review questions
Anon 2017[254]	Study/article does not address any of the call for evidence review questions
Anon 2018[602]	Not research article
Antcliff 2019[31]	Incorrect population (HCPs)
Antiel 2011[32]	Incorrect interventions (no intervention)
Armstrong 2012[33]	Study/article does not address any of the call for evidence review questions
Arnold 2015[34]	Incorrect study design (RCT)
Ates 2016[42]	Study/article does not address any of the call for evidence review questions
Augusto 2018[43]	Study/article does not address any of the call for evidence review questions
BACME 2019[47]	Incorrect population (survey of CFS/ME services)
Balaguru 2012[49]	Study/article does not address any of the call for evidence review questions
Baos 2019[51]	RCT protocol
Baraniuk 2017[53]	Study/article does not address any of the call for evidence review questions
Baraniuk 2018[52]	Study/article does not address any of the call for evidence review questions (BMJ best practice)
Barnden 2016[54]	Study/article does not address any of the call for evidence review questions
Bazelmans 2004[61]	Incorrect population (therapists)
Bazelmans 2005[62]	Incorrect study design (quantitative)
Bazilevskaya 2006[63]	Study/article does not address any of the call for evidence review questions
Belgian Ministry of Social Affairs, Public Health and Environment 2000[68]	Guidelines including systematic review of the evidence (unclear source of data on patient experience of CBT)
Bell 2016[69]	Letter/commentary/expert opinion
Berkovitz 2009[71]	Incorrect interventions (no intervention)

Study	Exclusion reason
Blease 2017[72]	Incorrect study design (review article)
Bloot 2015[76]	Incorrect study design (quantitative)
Blue Ribbon for the Awareness of Myalgic Encephalomyelitis 2010[77] (unpublished)	Incorrect study design (quantitative survey; no qualitative data)
Boneva 2019[78]	Incorrect interventions (no intervention)
Bould 2011[80]	Review
Bould 2013[79]	Not relevant to any call for evidence questions
Bowers 2019[82]	Study/article does not address any of the call for evidence review questions
Brigden 2018[87]	No intervention
Brigden 2018[84]	No relevant themes
Brigden 2016[86]	RCT protocol
Bringsli 2014[89]	Incorrect study design (quantitative survey)
Britain 2019 [91]	Conference abstract
Brooks 2011[97]	Incorrect study design (quantitative)
Broughton 2017[98]	Incorrect interventions (specialist services rather than specific interventions)
Brouwers 2002[99]	Incorrect study design (RCT)
Brown 2012[101]	Study/article does not address any of the call for evidence review questions
Brown 2005[103]	Study/article does not address any of the call for evidence review questions
Brown 2015[100]	Study/article does not address any of the call for evidence review questions
Buchachenko 2013[109]	Study/article does not address any of the call for evidence review questions
Buchachenko 2005[107]	Study/article does not address any of the call for evidence review questions
Buchachenko 2006[108]	Study/article does not address any of the call for evidence review questions
Buchachenko 2017[106]	Study/article does not address any of the call for evidence review questions
Buchachenko 2019[105]	Study/article does not address any of the call for evidence review questions
Burgess 2012[111]	Incorrect study design (RCT)
Burke 1986[113]	Study/article does not address any of the call for evidence review questions
Butland 1982[114]	Study/article does not address any of the call for evidence review questions
Calello 2018[115]	Study/article does not address any of the call for evidence review questions
Carpenter 2013[119]	Study/article does not address any of the call for evidence review questions
Carruthers 2011[122]	Study/article does not address any of the call for evidence review questions
Carruthers 2012[121]	Study/article does not address any of the call for evidence review questions
Carruthers 2003[120]	Guidelines

Study	Exclusion reason
Casanova 2011[123]	Study/article does not address any of the call for evidence review questions
Castro-Marrero 2016[126]	Incorrect study design (RCT)
Castro-Marrero 2017[125]	Study/article does not address any of the call for evidence review questions
Cella 2011[129]	Incorrect study design (quantitative)
Cella 2011[128]	Incorrect study design (quantitative)
Centers for Disease Control and Prevention 2019[130]	Study/article does not address any of the call for evidence review questions
CFS/ME National Outcomes Database Team 2016 [131]	Incorrect study design (non-comparative observational study)
CFS/ME Service for South Yorkshire and North Derbyshire 2019[132]	Incorrect study design (quantitative survey)
CFS/ME Service for South Yorkshire and North Derbyshire[133]	Incorrect study design (quantitative survey)
CFS/ME Working Group 2002[134] (unpublished)	No relevant themes
Chaudhuri 2003[149]	Study/article does not address any of the call for evidence review questions
Chalder 1993[136]	Study/article does not address any of the call for evidence review questions
Chalder 2010[138]	Incorrect study design (RCT)
Chalder 2010[135]	Incorrect study design (review, not qualitative)
Chalder 2015[140]	Incorrect study design (quantitative)
Chan 2019[146]	Not a qualitative study
Chang 2012[148]	Incorrect interventions (no intervention)
Childs 2019[158]	Incorrect study design (quantitative survey); no qualitative data
Chu 2018[162]	Study/article does not address any of the call for evidence review questions
Claypoole 2007[167]	Incorrect interventions (no intervention)
Cleare 2004[169]	Incorrect study design (quantitative)
Cliff 2019[171]	Study/article does not address any of the call for evidence review questions
Cockshell 2010[173]	Incorrect interventions (no intervention)
Collin 2018[179]	Study/article does not address any of the call for evidence review questions
Collin 2017[177]	Incorrect study design (non-comparative cohort study)
Collin 2017[175]	Incorrect study design (case-control)
Collin 2017[176]	Study/article does not address any of the call for evidence review questions
Collin 2016[180]	Study/article does not address any of the call for evidence review questions
Collin 2015[181]	Study/article does not address any of the call for evidence review questions
Collin 2012[182]	Incorrect study design (quantitative survey)
Collin 2011[178]	Study/article does not address any of the call for evidence review questions
Comhaire 2018[184]	Incorrect study design (quantitative)

Study	Exclusion reason
Cook 2017[185]	Incorrect interventions (no intervention)
Cooper 2019[186]	No relevant themes (qualitative data on an ME/CFS service, not specific interventions)
Corsius 2019[188]	Report summary; full report in Dutch
Costa 1995[189]	Study/article does not address any of the call for evidence review questions
Crawford 2010[195]	Study/article does not address any of the call for evidence review questions
Crawford 2012[194]	Letter/commentary/expert opinion
Crawford 2012[196]	Study advertisement
Crawley 2018[204]	Not relevant to monitoring/review question
Crawley 2013[200]	Incorrect interventions
Crawley 2013[198]	No relevant outcomes
Crawley 2011[203]	No intervention
Crawley 2009[199]	Study/article does not address any of the call for evidence review questions
Crawley 2009[202]	Study/article does not address any of the call for evidence review questions
Crowhurst 2005[205]	Letter/commentary/expert opinion
Crowhurst 2007[206]	No relevant themes
Currell[207]	No relevant themes (qualitative data on a specialist service, not specific interventions)
DARPA 2017[209]	Study/article does not address any of the call for evidence review questions
Davenport 2010[214]	Incorrect study design (conceptual model; not qualitative)
Davenport 2019[210]	Study/article does not address any of the call for evidence review questions
Davenport 2011[212]	Study/article does not address any of the call for evidence review questions
Davenport 2011[211]	Incorrect study design (quantitative)
Davenport 2019[213]	Letter/commentary/expert opinion
Davies 2008[215]	Study/article does not address any of the call for evidence review questions
Dawes 2019[255]	Executive summary of an excluded survey
Deale 2001[228]	Incorrect study design (RCT)
Deale 1998[227]	Incorrect study design (quantitative)
Deale 1997[225]	Incorrect study design (RCT)
De Becker 2000[219]	Study/article does not address any of the call for evidence review questions
De Becker 2001[217]	Study/article does not address any of the call for evidence review questions
Deftereos 2016[229]	Incorrect population (expert clinicians)
de Lange 2008[221]	Incorrect study design (quantitative)
DeLuca 2004[230]	Incorrect interventions (no intervention)
de Vega 2017[223]	Study/article does not address any of the call for evidence review questions
Devasahayam 2012[232]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Diao 2017[236]	Study/article does not address any of the call for evidence review questions
Dobson 2007[237]	Study/article does not address any of the call for evidence review questions
Dougall 2014[239]	Incorrect study design (RCT)
Doukrou 2019[240]	Incorrect study design (no qualitative data)
Dowsett 1997[241]	Study/article does not address any of the call for evidence review questions
Duyn 2017[243]	Study/article does not address any of the call for evidence review questions
Dyda 2018[245]	Study/article does not address any of the call for evidence review questions
Effective Health Care Program: Agency for Healthcare Research and Quality[248]	Systematic review protocol
Emerge Australia 2018[249]	Incorrect study design (quantitative survey)
Emerge Australia 2019[250]	Incorrect study design (quantitative survey)
Encephalitis Society 2017[251]	Study/article does not address any of the call for evidence review questions (website information)
Eroshenko 2004[252]	Study/article does not address any of the call for evidence review questions
Falk Hvidberg 2015[256]	Incorrect interventions (no intervention)
Faulkner 2016[257]	Letter/commentary/expert opinion
Fisher 2013[260]	No relevant themes
Fisk 1994[261]	Not relevant to any call for evidence questions
Flo 2014[262]	Incorrect study design (quantitative)
Fluge 2019[264]	Incorrect study design (RCT)
Fluge 2015[265]	Incorrect study design (quantitative)
Fluge 2016[263]	Study/article does not address any of the call for evidence review questions
Franklin 2018[268]	Incorrect study design (quantitative)
Fukuda 2016[274]	Incorrect study design (RCT)
Garner 2019[278]	Study/article does not address any of the call for evidence review questions
Geraghty 2018[282]	Incorrect study design (narrative review)
Geraghty 2016[284]	Incorrect study design (debate article)
Geraghty 2019[283]	Incorrect study design (literature review)
Geraghty 2019[280]	Letter/commentary/expert opinion
Geraghty 2017[279]	Incorrect study design (analysis of quantitative survey data)
Geraghty 2019[281]	Study/article does not address any of the call for evidence review questions
Ghatineh 2017[285]	Review of an RCT
Gielissen 2007[287]	Study/article does not address any of the call for evidence review questions
Gieré 2016[288]	Study/article does not address any of the call for evidence review questions
Gilder 2018[289]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Goedendorp 2009[293]	Study/article does not address any of the call for evidence review questions
Haig-Ferguson 2019[304]	No relevant themes
Haig-Ferguson 2009[305]	No relevant themes
Halapy 2017[306]	Letter/commentary/expert opinion
Harada 1999[309]	Study/article does not address any of the call for evidence review questions
Haywood 2012[317]	Study/article does not address any of the call for evidence review questions
Haywood 2014[316]	Systematic review with different PICO
Heald 2019[318]	Study/article does not address any of the call for evidence review questions
Healthwatch Trafford 2017[320]	No relevant themes
Healthwatch Lancashire 2017[319]	Different focus to review question
Heins 2013[322]	Incorrect study design (quantitative)
Heins 2013[321]	Incorrect study design (quantitative)
Heins 2011[323]	Incorrect study design (quantitative)
Heins 2010[324]	Incorrect study design (quantitative)
Hives 2017[326]	Incorrect study design (diagnostic accuracy study)
Hodges 2018[330]	Incorrect interventions (no intervention)
Holtzman 2019[331]	Study/article does not address any of the call for evidence review questions
Hughes 2002[339]	Review article
Hughes 2018[338]	Study/article does not address any of the call for evidence review questions
Huibers 2004[341]	Incorrect population (some met criteria for CFS, some did not and results not reported separately
Ickmans 2014[342]	Incorrect interventions (no intervention)
ICNIRP Project Group 2017[343]	Study/article does not address any of the call for evidence review questions
Ingman 2016[346]	Incorrect study design (quantitative)
Ingman[345]	Unable to obtain
Ingman[344]	Unable to obtain
Institute of Medicine 2015[347]	Study/article does not address any of the call for evidence review questions
ISRCTN Registry 2015[348]	Study/article does not address any of the call for evidence review questions
Jackson 2012[349]	Study/article does not address any of the call for evidence review questions
Janse 2019[350]	Prognostic study looking at predictors of outcome of CBT - none relevant to CFE questions
Janse 2019[352]	Incorrect study design (non-randomised quantitative study)
Janse 2018[354]	Incorrect study design (RCT)
Janse 2017[351]	Incorrect study design (RCT)
Janse 2016[353]	Incorrect population (idiopathic chronic fatigue); incorrect study design (RCT)
Janse 2015[355]	RCT protocol

Study	Exclusion reason
Jason 2006[357]	Study/article does not address any of the call for evidence review questions
Jason 2008[362]	Study/article does not address any of the call for evidence review questions
Jason 2009[356]	Incorrect study design (quantitative)
Jason 2009[358]	Study/article does not address any of the call for evidence review questions
Jason 2015[365]	Review article
Jason 2018[359]	Not relevant to any call for evidence question
Jelinek 2001[367]	Study/article does not address any of the call for evidence review questions
Jenkins 2005[368]	Study/article does not address any of the call for evidence review questions
Jones 2012[372]	Incorrect study design (quantitative)
Josev 2019[374]	Incorrect interventions (no intervention)
Juutilainen 2018[376]	Study/article does not address any of the call for evidence review questions
Kapitein 2015[377]	Study/article does not address any of the call for evidence review questions
Kasevich 2002[378]	Study/article does not address any of the call for evidence review questions
Keller 2014[381]	Incorrect interventions (no intervention)
Kempke 2013[382]	Study/article does not address any of the call for evidence review questions
Kenyon 2019[384]	Incorrect study design (quantitative)
Kim 2019[390]	Study/article does not address any of the call for evidence review questions
Kindlon 2011[399]	Letter/commentary/expert opinion
Kindlon 2017[393]	Letter/commentary/expert opinion
Kindlon 2009[392]	Letter/commentary/expert opinion
Kindlon 2010[401]	Letter/commentary/expert opinion
Kindlon 2010[403]	Letter/commentary/expert opinion
Kindlon 2011[395]	Letter/commentary/expert opinion
Kindlon 2012[396]	Letter/commentary/expert opinion
Kindlon 2012[397]	Letter/commentary/expert opinion
Kindlon 2015[394]	Letter/commentary/expert opinion
Kindlon 2015[402]	Letter/commentary/expert opinion
Kindlon 2015[404]	Letter/commentary/expert opinion
Kindlon 2011[398]	Letter/commentary/expert opinion
Kindlon 2009[400]	Letter/commentary/expert opinion
Kingdon 2018[406]	Study/article does not address any of the call for evidence review questions
Knoester 2019[409]	Study/article does not address any of the call for evidence review questions
Knoop 2008[414]	Incorrect study design (RCT)
Knoop 2007[413]	Incorrect study design (quantitative)
Knoop 2007[411]	Incorrect study design (quantitative)
Knoop 2007[410]	Incorrect study design (quantitative)

Study	Exclusion reason
Knoop 2008[412]	Incorrect study design (RCT)
Knudsen 2011[416]	Study/article does not address any of the call for evidence review questions
Kodama 2013[417]	Study/article does not address any of the call for evidence review questions
Kreyberg 2007[420]	Guidelines
Kreyberg 2007[421]	Incorrect population (nursing staff)
Lacerda 2018[422]	Study/article does not address any of the call for evidence review questions
Lacerda 2019[423]	No relevant themes
LaManca 1998[424]	Incorrect interventions (no intervention)
Lapp 2019[426]	Letter/commentary/expert opinion
Larun 2014[432]	Incorrect study design (systematic review of RCTs)
Leaman 1997[434]	Study/article does not address any of the call for evidence review questions
Leone 2006[440]	Not relevant to any call for evidence question
Lewis 2013[442]	Incorrect interventions (no intervention)
Lien 2019[447]	Study/article does not address any of the call for evidence review questions
Light 2009[448]	Incorrect study design (quantitative)
Lincolnshire Partnership 2019[450]	Qualitative data in the form of quotes - no thematic analysis
Liu 2018[455]	Study/article does not address any of the call for evidence review questions
Lloyd 2012[458]	Incorrect study design (quantitative)
Lloyd 2012[457]	Incorrect study design (RCT)
Loades 2016[462]	Systematic review with different PICO
Loades 2019[459] (unpublished)	Incorrect population (already diagnosed with ME/CFS); incorrect study design (cross-sectional epidemiological study with no interventions)
Loades 2019[463]	Incorrect study design (qualitative); also excluded from experiences of interventions review due incorrect population (healthcare professionals)
Loades 2019[460]	Incorrect study design (quantitative)
Loades 2018[461]	Study/article does not address any of the call for evidence review questions
Loy 2016[467]	Incorrect study design (quantitative)
Lyshevski 2001[469]	Study/article does not address any of the call for evidence review questions
Maes 2006[472]	Study/article does not address any of the call for evidence review questions
Maes 2009[473]	Study/article does not address any of the call for evidence review questions
Maes 2012[474]	Study/article does not address any of the call for evidence review questions
Marshall 1997[482]	Not relevant to any call for evidence question
Marshall 1996[483]	Incorrect study design (quantitative)
Mathew 2009[485]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
May 2010[486]	Study/article does not address any of the call for evidence review questions
McCourt 2019[487]	Study/article does not address any of the call for evidence review questions
McDermott 2006[492]	Study/article does not address any of the call for evidence review questions
McGregor 2016[493]	Study/article does not address any of the call for evidence review questions
McGregor 2019[494]	Study/article does not address any of the call for evidence review questions
McManimen 2016[498]	Study/article does not address any of the call for evidence review questions
McPhee 2019[499]	Qualitative section was related to information given to patients about possible harms, data about harm was quantitative
ME/cvs Vereniging 2016[500]	Report summary; full report in Dutch
Meeus 2015[501]	Incorrect study design (RCT)
ME Group 2019[471]	No qualitative findings/data analysis reported
ME Group 2014[470]	No qualitative findings/data analysis reported
Melamed 2019[504]	Study/article does not address any of the call for evidence review questions
Mihelicova 2016[508]	No relevant themes
Miller 2015[510]	Study/article does not address any of the call for evidence review questions
Millions Missing Canada 2017[511]	Incorrect study design (quantitative survey)
Missen 2012[512]	No relevant outcomes
Moneghetti 2018[513]	Incorrect interventions (no intervention)
Montoya 2018[514]	Incorrect study design (RCT)
Montoya 2013[515]	Incorrect study design (RCT)
Moore 2000[516]	Study/article does not address any of the call for evidence review questions
Moore 2015[517]	Study/article does not address any of the call for evidence review questions
Morens 2019[518]	Study/article does not address any of the call for evidence review questions
Morris 2014[519]	Study/article does not address any of the call for evidence review questions
Murdock 2017[522]	Study/article does not address any of the call for evidence review questions
Myalgic Encephalomyelitis / Chronic Fatigue Syndrome Advisory Committee 2019[523]	Study/article does not address any of the call for evidence review questions
Nacul 2011[526]	Study/article does not address any of the call for evidence review questions
Nacul 2011[527]	Study/article does not address any of the call for evidence review questions
Nacul 2018[528]	Study/article does not address any of the call for evidence review questions
Nacul 2019[525]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Nacul 2019[524]	Study/article does not address any of the call for evidence review questions
Nagy-Szakal 2018[529]	Study/article does not address any of the call for evidence review questions
Natelson 2017[531]	Study/article does not address any of the call for evidence review questions
Natelson 2017[530]	Study/article does not address any of the call for evidence review questions
National Centers for Environmental Information[532]	Study/article does not address any of the call for evidence review questions
National Collaborating Centre for Primary Care 2007[533]	Study/article does not address any of the call for evidence review questions
Naviaux 2016[536]	Study/article does not address any of the call for evidence review questions
Naviaux 2017[535]	Study/article does not address any of the call for evidence review questions
Newberry 2018[537]	Study/article does not address any of the call for evidence review questions
Newton 2010[538]	Study/article does not address any of the call for evidence review questions
NHS North Bristol 2019[540]	No relevant themes (qualitative data on specialist services, not specific interventions)
Nijhof 2014[544]	Incorrect study design (quantitative)
Nijhof 2013[543]	Incorrect study design (quantitative)
Nijhof 2012[541]	Incorrect study design (RCT)
Nijhof 2011[542]	RCT protocol
Norfolk and Suffolk Service 2009[547]	Unable to obtain (web link unavailable)
Norris 2017[548]	Incorrect study design (cross-sectional analysis of quantitative data)
Ocon 2012[554]	Study/article does not address any of the call for evidence review questions
Odoom 2018[555]	Study/article does not address any of the call for evidence review questions
Office for National Statistics 2018[556]	Not relevant to any call for evidence questions
Ojo-Amaize 1994[557]	Study/article does not address any of the call for evidence review questions
Oliver 2018[559]	Incorrect study design (quantitative survey)
PACE Trial participant dataset[565]	Study/article does not address any of the call for evidence review questions
Packer 1997[566]	Study/article does not address any of the call for evidence review questions
Pakpoor 2017[567]	Study/article does not address any of the call for evidence review questions
Parslow 2018[570]	No relevant themes
Parslow 2017[572]	Incorrect study design (qualitative)
Parslow 2017[571]	Systematic review with different PICO
Parslow 2015[569]	Incorrect study design (qualitative; assessed for monitoring and review question)

Study	Exclusion reason
Pastula 2014 [573]	Study/article does not address any of the call for evidence review questions
Patrick Neary 2008[576]	Incorrect interventions (no intervention)
Peci 2015[577]	Study/article does not address any of the call for evidence review questions
Peckerman 2003[578]	Study/article does not address any of the call for evidence review questions
Pemberton 2014[580]	No relevant themes
Pemberton 2014[579]	No relevant themes
Peterson 1991[585]	Not relevant to any call for evidence question
Peterson 1994[586]	Incorrect interventions (no intervention)
Perrin 1993[582]	Review; study/article does not address any of the call for evidence review questions
Perrin 1998[583]	Incorrect study design (non-randomised quantitative study)
Perrin 2011[584]	Incorrect study design (non-randomised quantitative study)
Pheby 2009[587]	Incorrect study design (survey) and no useable data
Plascencia-Villa 2016[594]	Study/article does not address any of the call for evidence review questions
Polli 2019[596]	Incorrect study design (quantitative)
Polo 2019[598]	Incorrect study design (no qualitative data)
Prins 2005[605]	Incorrect study design (quantitative)
Prins 2001[606]	Incorrect study design (RCT)
Prokhorov 2016[608]	Study/article does not address any of the call for evidence review questions
Puri 2011[610]	Incorrect study design (diagnostic accuracy study)
Quarmby 2007[611]	Incorrect study design (quantitative)
Raine 2004[613]	Incorrect population (GPs)
Rand Corporation[614]	Study/article does not address any of the call for evidence review questions
Rawlins 2008[616]	Study/article does not address any of the call for evidence review questions
Regland 2015[620]	Incorrect study design (quantitative)
Reynolds 2014[625]	Incorrect interventions (no intervention)
Richardson 2002[629]	Review article
Rimes 2014[634]	Incorrect study design (quantitative)
Roberts 2016[638]	Study/article does not address any of the call for evidence review questions
Roberts 2009[636]	Incorrect study design (quantitative)
Roberts 2018[637]	Study/article does not address any of the call for evidence review questions
Roe[639]	No relevant themes (qualitative data on a specialist service, not specific interventions)
Roerink 2017[642]	Study/article does not address any of the call for evidence review questions
Roerink 2017[640]	Incorrect study design (RCT)
Roerink 2015[641]	RCT protocol
Roma 2019[643]	Incorrect interventions (no intervention)

Study	Exclusion reason
Rowe 2019[648]	Incorrect study design (questionnaire with closed and open ended questions; no thematic analysis)
Rowe 2017[649]	Review article
Ruggieri 2017[650]	Study/article does not address any of the call for evidence review questions
Santini 2018[659]	Study/article does not address any of the call for evidence review questions
Ŝarić 2016[660]	Study/article does not address any of the call for evidence review questions
Scheeres 2009[662]	Study/article does not address any of the call for evidence review questions
Scheeres 2008[664]	Incorrect study design (quantitative)
Scheeres 2008[663]	Incorrect study design (quantitative)
Scheeres 2007[665]	Study/article does not address any of the call for evidence review questions
Schmaling 2019[666]	Study/article does not address any of the call for evidence review questions
Schweitzer 1995[668]	Not relevant to any call for evidence question
Severens 2004[671]	Letter/commentary/expert opinion
Shakespeare 2017[672]	Study/article does not address any of the call for evidence review questions
Shan 2018[673]	Study/article does not address any of the call for evidence review questions
Sharpe 1991[679]	Study/article does not address any of the call for evidence review questions
Sharpe 2015[676]	Incorrect study design (RCT)
Shukla 2015[681]	Incorrect study design (quantitative)
Shungu 2012[682]	Study/article does not address any of the call for evidence review questions
Smith 2014[685]	Incorrect study design (systematic review of RCTs)
Smith 2013[687]	Systematic review with different PICO
Smith 2015[684]	Incorrect study design (systematic review of RCTs)
Snell 2013[688]	Study/article does not address any of the call for evidence review questions
Solomon-Moore 2019[694]	Incorrect study design (baseline cross-sectional data from an RCT)
Stahl 2014[696]	Incorrect study design (quantitative)
Staud 2017[698]	Incorrect study design (RCT)
Staud 2018[697]	Incorrect study design (quantitative)
Steffen 2002[699]	Study/article does not address any of the call for evidence review questions
Stevelink 2019[701]	Study/article does not address any of the call for evidence review questions
Stevens 2018[703]	Study/article does not address any of the call for evidence review questions
Stevens 2010[704]	Incorrect study design (case study)
Stoll 2017[705]	Systematic review with different PICO
Stordeur 2008[706]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Strassheim 2018[710]	Study/article does not address any of the call for evidence review questions
Strawbridge 2019[711]	Not relevant to any call for evidence question
Strayer 2012[712]	Incorrect study design (RCT)
Strbak 2011[713]	Study/article does not address any of the call for evidence review questions
Stulemeijer 2005[716]	Incorrect study design (RCT)
Sumathipala 2008[718]	Incorrect population (medically unexplained symptoms)
Sunnquist 2018[720]	Incorrect study design (quantitative)
Suvorov 1998[725]	Study/article does not address any of the call for evidence review questions
Swinscow 1997[726]	Study/article does not address any of the call for evidence review questions
Taylor 2004[732]	Incorrect study design (RCT)
Taylor 2019 Leeds and York CFS/ME Service[730] (unpublished)	No qualitative data
Taylor 2016[729]	Study/article does not address any of the call for evidence review questions
Teitelbaum 2001[737]	Incorrect study design (RCT)
Terzi 2016[738]	Study/article does not address any of the call for evidence review questions
The 2010[752]	Incorrect study design (RCT)
The 2007[753]	Incorrect study design (RCT)
The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee 1997[751]	Not relevant to any call for evidence questions
The 25% ME Group 2010[740]	Different focus to review question
The 25% ME Group 2014[741] (unpublished)	Report on a research presentation; no qualitative data from people with ME/CFS
The 25% ME Group 2004[750]	Incorrect study design (quantitative survey)
The 25% ME Group 2000[747]	Incorrect study design (quantitative survey)
The 25% ME Group 2001[742]	Incorrect study design (quantitative survey)
The 25% ME Group[749]	Article; no qualitative data from people with ME/CFS
The 25% ME Group 2002[746] (unpublished)	Incorrect study design (quantitative survey)
The 25% ME Group 2017[744]	Not relevant to any call for evidence questions
The 25% ME Group 2018[743]	Not relevant to any call for evidence questions
The 25% ME Group 2001[745]	Incorrect study design (quantitative survey)
The 25% ME Group 2016[748]	Study/article does not address any of the call for evidence review questions (newsletter)
The ME Association 2010[754]	Incorrect study design (quantitative survey)
The ME Association 2015[755]	Survey including quantitative and qualitative data, but no analysis on the qualitative data
The Neurological Alliance 2019[756]	Incorrect study design (quantitative survey)
Thomas 2009[758]	Incorrect interventions (no intervention)
Tiersky 2001[760]	Incorrect study design (quantitative)

Study	Exclusion reason
Timbol 2019[761]	No relevant themes
Togo 2015[762]	Incorrect interventions (no intervention)
Trabal 2012[764]	Study/article does not address any of the call for evidence review questions
Tummers 2013[770]	Incorrect study design (quantitative)
Tummers 2012[769]	Incorrect study design (RCT)
Tummers 2010[768]	Incorrect study design (quantitative)
Twisk 2014[775]	Letter/commentary/expert opinion
Twisk 2017[772]	Letter/commentary/expert opinion
Twisk 2018[771]	Report summary; full report in Dutch
Twisk 2015[774]	Study/article does not address any of the call for evidence review questions
Twisk 2015[773]	Incorrect study design (review article)
Van Campen 2018[776]	Incorrect interventions (no intervention)
Van Campen 2018[778]	Study/article does not address any of the call for evidence review questions
Van Campen 2019[777]	Incorrect study design (quantitative)
Van Den Eede 2011[780]	Study/article does not address any of the call for evidence review questions
Van Der Schaaf 2015[783]	RCT protocol
Van Der Schaaf 2017[782]	Study/article does not address any of the call for evidence review questions
Van Der Werf 2002[785]	Study/article does not address any of the call for evidence review questions
Van Konynenburg 2010[788]	Conference abstract
Van Kuppeveld 2010[789]	Study/article does not address any of the call for evidence review questions
VanNess 2007[790]	Incorrect interventions (no intervention)
VanNess 2010[791]	Incorrect intervention (exercise test)
Velleman 2016[792]	Incorrect population (siblings) and no relevant themes
Vercoulen 1996[794]	Incorrect study design (RCT)
Vercoulen 1996[793]	Study/article does not address any of the call for evidence review questions
Vermeulen 2010[795]	Study/article does not address any of the call for evidence review questions
Vermeulen 2014[797]	Study/article does not address any of the call for evidence review questions
Vernon 2004[798]	Unable to obtain
Verspaandonk 2015[799]	Incorrect study design (quantitative)
Vink 2017[801]	Incorrect study design (quantitative)
Vink 2018[804]	Review of an RCT
Vink 2018[803]	Incorrect study design (reanalysis of a Cochrane review); no qualitative data
Vink 2019[805]	Review article
Vink 2019[802]	Incorrect study design (reanalysis of a Cochrane review); no qualitative data
Wallis 2016[813]	Study/article does not address any of the call for evidence review questions

Study	Exclusion reason
Wallis 2018[812]	Incorrect study design (quantitative)
Wang 2017[818]	Study/article does not address any of the call for evidence review questions
Watt 2012[831]	Incorrect study design (quantitative)
Wearden 2006[837]	Study/article does not address any of the call for evidence review questions
Wearden 2010[834]	Incorrect study design (RCT)
Wearden 2013[835]	Incorrect study design (prognostic)
Webb 2011[840]	No relevant themes
Werbach 2000[841]	Incorrect study design (literature review)
White 2007[848]	RCT protocol
White 2011[847]	Incorrect study design (RCT)
White 2013[846]	Study/article does not address any of the call for evidence review questions
Whitehead 2009[849]	Study/article does not address any of the call for evidence review questions
Whitehead 2002[851]	Study/article does not address any of the call for evidence review questions
Wiborg 2010[855]	Incorrect study design (reanalysis of RCTs)
Wiborg 2014[857]	Incorrect study design (quantitative)
Wiborg 2015[856]	Incorrect study design (RCT)
Wiborg 2011[854]	Incorrect study design (quantitative)
Wieczorek 2017[817]	Study/article does not address any of the call for evidence review questions
Wilshire 2018[864]	Incorrect study design (reanalysis of an RCT)
Wilshire 2019[863]	Letter/commentary/expert opinion
Wilshire 2017[861]	Incorrect study design (critical commentary and reanalysis of an RCT)
Wilshire 2017[862]	Letter/commentary/expert opinion
Worm-Smeitink 2019[871]	Incorrect study design (RCT)
Worm-Smeitink 2017[870]	Study/article does not address any of the call for evidence review questions
Worm-Smeitink 2016[872]	Incorrect study design (quantitative)
Zablotskii 2016[880]	Study/article does not address any of the call for evidence review questions
Zablotskii 2018[881]	Study/article does not address any of the call for evidence review questions
Zhi 2017[888]	Study/article does not address any of the call for evidence review questions
Zielinski 2019[891]	Study/article does not address any of the call for evidence review questions

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