National Institute for Health and Care Excellence

FINAL

Depression in adults

[B] Treatment of a new episode of depression

NICE guideline NG222

Evidence reviews underpinning recommendations 1.5.2 to 1.5.3, 1.6.1, 1.7.1 and research recommendations in the NICE guideline

June 2022

Final

May 2024: We have simplified the guideline by removing recommendations on general principles of care that are covered in other NICE guidelines (for example, the NICE guideline on service user experience in adult mental health).

This is a presentational change only, and no changes to practice are intended.

Disclaimer

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Treatment of a new episode of depression

This evidence review contains 2 reviews relating to treatment of a new episode of depression.

- Review question 2.1 For adults with a new episode of less severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?
- Review question 2.2 For adults with a new episode of more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Introduction

There is a wide range of interventions available to treat depression, including pharmacological, psychological, psychosocial and physical interventions. The range of options is further extended as different treatment modalities may be used in combination with each other, leading to a large number of possible permutations.

To inform the choice of intervention, or combination of interventions, knowledge of the relative benefits, harms and costs is essential. It is particularly important to know if combinations of treatments offer any advantages as they are likely to be more resource-intensive and more onerous to patients.

In addition to the complexity introduced by the number of available interventions, the choice of treatment for a new episode of depression may also depend on its severity. In order to address this, the analysis has been sub-divided to identify interventions that are most effective for less severe depression (mild and subthreshold depression), and those that are most effective for more severe depression (moderate and severe depression). The criteria used to define ‘less severe’ and ‘more severe’ depression are described below and in the review protocol (appendix A).

The aim of this review is to compare the effectiveness, acceptability and tolerability of treatments for a new episode of less severe or more severe depression, including a range of pharmacological, psychological, psychosocial and physical interventions.

Summary of the interventions included in this evidence review

Due to the large number of different treatment options considered in this review, they have been grouped into classes to allow comparison between classes of treatment. For example, psychological therapies are grouped according to common theoretical structure and methodological approach, and pharmacological treatments are grouped according to mechanism of action or chemical structure. Further details about the classes and interventions included in each class are provided in Supplement B1 (Interventions and classes).

For inclusion in this review, the committee agreed that pharmacological interventions needed to be licensed in the UK and in routine clinical use for the first-line treatment of depression. The national prescription data for England in 2017 (Prescribing & Medicines Team, Health and Social Care Information Centre, 2017) was used to define routine usage of drugs: if a drug appeared in the top 15 antidepressants prescribed by volume it was included, with the exception of dosulepin which the BNF indicates should be initiated by a specialist.

Some interventions were included in the evidence review to improve connectivity within the network meta-analysis but were not considered as part of the decision problem, so were not considered as candidates for recommendations. If necessary for connectivity in the network, excluded pharmacological interventions were added as ‘any antidepressant’ or ‘any SSRI’ or

'any TCA' nodes but only where the pharmacological interventions had been compared against an included psychological or physical intervention and/or combined with an included psychological or physical intervention. This approach is outlined in the review protocol (appendix A).

For psychological interventions, the committee were interested in exploring whether there was a difference in the effects of briefer relative to longer interventions. This differentiation by intensity (number of sessions) was possible for CBT because there was large variation in the number of sessions reported across RCTs, and there was also a large evidence base that allowed formation of 2 separate groups of interventions according to the number of sessions offered. It was not possible to create distinct intervention categories based on intensity for other interventions because there was either no great variation in the number of sessions reported for an intervention in the RCTs included, or the evidence base was too narrow. For each level of severity, for the class of Cognitive and cognitive behavioural therapies, both individual and group, the NMA classification system made a distinction between CBT ≥15 sessions and CBT<15 sessions, which were considered as separate interventions within the class.

Couple interventions, including behavioural couple's therapy, were considered more appropriate for subgroups of adults with depression, namely for people with problems in the relationship with their partner, and as such these interventions were considered only in pairwise comparisons (and not included in the network meta-analysis).

Summary of the protocol

See **Error! Reference source not found.** for a summary of the Population, Intervention, C omparison and Outcome (PICO) characteristics of this review.

Table 1. Summary of the protocol (PICO table)

Population	Adults receiving first-line treatment for a new episode of depression, as defined by a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by baseline depression scores on validated scales (and including those with subthreshold [just below threshold] depressive symptoms). If some, but not all, of a study's participants are eligible for the review, for instance, mixed anxiety and depression diagnoses, then we will include a study if at least 80% of its participants are eligible for this review. Baseline mean scores are used to classify study population severity according to less severe (RQ 2.1) or more severe (RQ 2.2).
Intervention	**Psychological interventions:** • Behavioural therapies • Cognitive and cognitive behavioural therapies • Counselling • Interpersonal psychotherapy • Psychodynamic psychotherapies • Psychoeducational interventions • Self-help with or without support • Art therapy

	• Music therapy • Eye movement desensitization and reprocessing (for depression, not PTSD) • Couple interventions (pairwise only) **Pharmacological interventions**: • SSRIs ○ Citalopram ○ Escitalopram ○ Paroxetine ○ Sertraline ○ Fluoxetine • TCAs ○ Amitriptyline ○ Clomipramine ○ Lofepramine ○ Nortriptyline ○ (imipramine included to improve connectivity but not part of the decision problem) • SNRIs ○ Venlafaxine ○ Duloxetine • Other antidepressant drugs ○ Mirtazapine ○ Trazodone (for specific drugs that are excluded, 'any antidepressant', 'any SSRI' or 'any TCA' nodes may be added where they have been compared against a psychological or physical intervention and/or combined with a psychological or physical intervention, but they will not be considered as part of the decision problem) **Physical interventions:** • Acupuncture • Exercise (including yoga) • Light therapy (for depression, not SAD) **Psychosocial interventions:** • Peer support • Mindfulness, meditation or relaxation
Comparator	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo
Outcomes	**Critical:**

	• Depression symptomatology • Remission (usually defined as a cut off on a depression scale) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) • Discontinuation due to side effects (for pharmacological trials) • Discontinuation due to any reason (including side effects) **Important:** • Quality of life • Personal, social and occupational functioning

DSM: Diagnostic and statistical manual of mental disorders; ICD: international classification of diseases; PTSD: post-traumatic stress disorder; SAD: seasonal affective disorder; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and methods specific to the NMA are summarised below, and described in appendix M and in supplement 1 - Methods.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Summary of methods

Defining less and more severe depression

Baseline mean scores on validated depression scales were used to classify study population severity according to less severe (review question 2.1) or more severe (review question 2.2) using the thresholds outlined in the review protocol (appendix A). These thresholds were derived using standardization of depression measurement crosswalk tables (Carmody 2006; Rush 2003; Uher 2008; Wahl 2014). An anchor point of 16 on the PHQ-9 was selected as the cut-off between less severe and more severe depression, on the basis of alignment with the clinical judgement of the committee and eligibility criteria in published studies. If baseline mean scores were not available, severity was classified according to the inclusion criteria of the study or the description given by the study authors (but only in cases where this is unambiguous, for example 'severe' or 'subthreshold' or 'mild'). The category of less severe depression used in this guideline includes the traditional categories of subthreshold symptoms and mild depression, and the category of more severe depression used in this guideline includes the traditional categories of moderate and severe depression.

Evidence synthesis

The main method used to synthesise evidence on pharmacological, psychological, psychosocial, physical and combined interventions included in this review was network meta-analysis (NMA). NMA is a generalisation of standard pairwise meta-analysis for A versus B

trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (Dias 2011a; Lu 2004).

NMA was employed to assess the following outcomes:

- Clinical analysis - critical outcomes:
  - Standardised mean difference (SMD) of depression symptom change scores at treatment endpoint; this was selected as the primary critical outcome
  - Response in those randomised at treatment endpoint (also known as 'intention to treat' or 'ITT')
  - Remission in those randomised at treatment endpoint (also known as 'intention to treat' or 'ITT')
- Economic analysis:
  - Acceptability: treatment discontinuation for any reason at treatment endpoint in those randomised
  - Tolerability: treatment discontinuation due to side effects from medication at treatment endpoint in those who discontinued treatment; this outcome was only relevant to interventions with a pharmacological element.
  - Response at treatment endpoint in those who completed treatment (also known as 'completers')
  - Remission at treatment endpoint in those who completed treatment (also known as 'completers')

Pairwise meta-analysis was undertaken to assess the following outcomes, as there was not enough evidence to create a network:

- Quality of life
- Personal, social, and occupational functioning including global functioning, functional impairment, sleeping difficulties, employment, interpersonal problems
- Follow-up data on critical outcomes for the clinical analysis.

In addition, pairwise meta-analysis was employed to synthesise data on all critical outcomes of the clinical analysis (SMD, response in those randomised, remission in those randomised). The aim of this analysis was to compare the results of the NMA with those of pairwise meta-analysis and explore any differences between them and possible reasons for any differences However, results of these pairwise meta-analyses were not considered as a primary source of evidence when formulating recommendations.

SMD was used as a summary statistic as data were synthesised across a number of depression scales. For all scales, the score increased with symptom severity, therefore no transformation was required to correct for differences in the direction of the scales.

Class models

Due to the large number of interventions included in this review, comparing all pairs of interventions individually within the NMA (and also in the pairwise meta-analysis) would not be feasible and would require particularly complex consideration and interpretation of the NMA evidence. Moreover, some interventions included in the systematic review had been tested on small numbers of participants and their effects were characterised by considerable uncertainty. For these reasons, the NMAs utilised class models: each class consisted of interventions with a similar mode of action or similar treatment components or approaches, so that interventions within a class were expected to have similar (but not necessarily identical) effects. Use of class models in the NMA had three benefits:

- strength could be borrowed across interventions in the same class, therefore improving precision of effects

- networks that were otherwise disconnected were possible to connect via interventions belonging to the same class, resulting in a connected network that included all classes and interventions of interest
- relative effects between a more limited number of classes were easier to interpret and thus more helpful for the committee when making recommendations.

Following appropriate tests of fit, random class effect models were used for all outcomes examined in the NMAs, which assume that the effects of interventions in a class are distributed around a common class mean with a within-class variance. Under this approach individual treatment effects are drawn towards a class mean but individual intervention estimates that are more precise can still be estimated.

Bias adjustment NMA models and other sensitivity analyses

A key assumption in NMA is that of transitivity – that is, that the balance of effect modifiers (factors that influence the treatment effect) is similar across all trials in the network. In order to explore the validity of this assumption, several pre-specified sensitivity analyses were conducted.

Publication bias is known to affect results of meta-analyses in several clinical areas, including depression (Driessen 2015; Moreno 2009 & 2011; Trinquart 2012; Turner 2008). Small sample size studies are associated with publication bias as small studies with positive results are more likely to be published compared with small studies with negative results, and may also be associated with lower study quality. Published smaller studies tend to overestimate the relative treatment effect of interventions versus control, compared to larger studies (Chaimani 2013; Moreno 2011). Furthermore, small studies are often of poorer quality, and may be at higher risk of bias, which can lead to inflated estimates of efficacy and violate the transitivity assumption.

As the NMAs included a significant number of small studies, sensitivity analyses were carried out on selected outcomes, which adjusted for bias associated with small study size effects. The analyses, which were based on the assumption that the smaller the study the greater the bias, attempted to estimate the “true” treatment effect that would be obtained in a study of infinite size. The analyses assumed possible bias in comparisons of active interventions versus inactive control and no bias between inactive control comparisons, as well as between active intervention comparisons. The exception to this was in comparisons where non-directive counselling was the control intervention (in which case bias against non-directive counselling was assumed). This exception was based on committee and stakeholder concerns that non-directive counselling when used as a control intervention may be less likely to be manual-based, and to be delivered in a comparable number of sessions by an equivalent healthcare professional as when non-directive counselling is included as an active intervention in trials. Bias adjustment assumptions were supported by empirical evidence of the direction and magnitude of small study bias in meta-analyses of psychological interventions versus control (Driessen 2015) and of antidepressants versus pill placebo (Turner 2008).

Bias adjustment models were developed for the following outcomes synthesised in NMAs:

- SMD of depression symptom change scores (primary critical outcome for clinical analysis)
- Treatment discontinuation for any reason in those randomised
- Response in completers

The latter two outcomes were selected for bias adjustment because they were the main NMA outcomes that informed the economic analysis, with the highest anticipated impact on the results. Subsequently, where bias was identified, an economic probabilistic sensitivity analysis was conducted using the outputs of the bias-adjusted NMAs on these two outcomes, as relevant (see appendix J).

In addition, the validity of the transitivity assumption between participants in pharmacological trials and participants in non-pharmacological trials was explored by a sensitivity analysis on the SMD outcome that included non-pharmacological trials only and examined any differences in magnitude of effects and ranking of non-pharmacological interventions compared to results from the mixed psychological, psychosocial, pharmacological and physical model that utilised the full study dataset.

Moreover, a post-hoc sensitivity analysis that included only RCTs rated as being at low risk of bias according to the Cochrane risk of bias tool version 1.0 for RCTs (see appendix H in Developing NICE guidelines: the manual) was conducted on the SMD outcome, which was the primary critical outcome of the clinical analysis. Such analysis was only possible to conduct for the domain of 'attrition' in the risk of bias tool, as this was the only domain that included a sufficient number of RCTs at low risk of bias, and a relatively wide range of treatment classes.

Several other post-hoc sensitivity analyses were also conducted to explore the validity of the transitvity assumption in more detail (see appendix M). These investigated the impact of removing small studies or studies with >5 points contribution to the residual deviance from the analysis, and assuming additivity of treatments combined with TAU.

Presentation of the NMA results

The NMAs undertaken to address the 2 review questions covered in this report (treatments for a new episode of less severe depression and treatments for a new episode of more severe depression) included 676 studies comparing 63 classes of 152 pharmacological, psychological, psychosocial and physical interventions alone or in combination as well as controls; 51 of these classes represented active treatment options that were part of the decision problem, meaning they were candidates for recommendation.

Results of the NMAs are presented in the main report as the posterior mean SMD of depression symptom change scores (continuous data) or log-odds ratios (LORs) (for dichotomous data), as appropriate, with 95% Credible Intervals (CrI) compared with the reference treatment. For the analysis of treatments for less severe depression the selected reference treatment was treatment as usual (TAU), whereas for the analysis of treatments for more severe depression the selected reference treatment was pill placebo. Selection of reference treatments was made following inspection of the size of the evidence and the connectivity of control treatments in each population, and considering control treatments with their own established effects. The committee expressed a preference for pill placebo as it is well-defined across trials. On the other hand, the definition of TAU may vary across trials, although it has been widely used as the control treatment in meta-analyses of psychological trials. The committee considered the comparisons of psychological treatment classes and interventions with pill placebo as an advantage of conducting the NMAs, because psychological therapies are not routinely compared with pill placebo, unless active drug arms are included in the trial. A further advantage of selecting pill placebo is that it provides a more conservative estimate and convincing comparison for clinical effect and addresses treatment expectancy effects for interventions. Nevertheless, pill placebo was tested on a very small number of people in less severe depression and it had limited connectivity (or was completely absent) in most network plots in this population. Therefore, its use as a reference was considered inappropriate and TAU was selected instead as the next best option to serve as reference in NMAs of treatments for less severe depression. No treatment and waitlist were considered to have a minimal effect and to potentially hinder other underlying interventions and therefore were deemed inappropriate baseline comparators.

The main body of the report provides NMA results at the treatment class level for all critical outcomes included in the clinical analysis. Rankings have been calculated only for treatment classes of interest (classes that were part of the decision problem). For the SMD of depression symptom change scores, which was the primary critical efficacy outcome, results of individual interventions are also provided for information.

An overview of the results on outcomes used in the economic analysis are reported in appendix J.

Results of the NMAs on all outcomes that informed the clinical and the economic analysis, including relative effects for all pairs of treatment classes and interventions included in the NMA, are reported in appendix M and supplements B5 and B6.

Presentation of the pairwise meta-analysis results

In accordance with the data analysis strategy outlined in the review protocol (see appendix A), the NMA results were the primary input for clinical decision-making (and were considered alongside the results from the economic models when developing recommendations). Pairwise meta-analyses were used as follows:

- to analyse important (but not critical) outcomes, and follow-up of critical outcomes, which could not be included in NMA due to a lack of connectivity in the networks for these outcomes and time points
- to compare the results of pairwise meta-analysis with the NMA for critical outcomes
- to analyse interventions that are only appropriate for sub-groups of people with depression (and not included in the NMA), specifically couple interventions for those with problems in the relationship with their partner
- to undertake subgroup analysis of studies included in the NMA. Planned subgroup analyses (provided sufficient data were available) included: older adults (60 years and older) compared to younger adults (younger than 60 years); BME populations; men. Additional subgroup analyses (primary care compared to secondary care; inpatient compared to outpatient settings) were planned to inform the evidence review on settings for care but were not considered for recommendations for first-line treatment of less severe and more severe depression.

For pairwise comparisons, meta-analyses using random-effects models were conducted to combine results from similar studies. An intention to treat (ITT) approach was taken where possible. Continuous outcomes were assessed using standardized mean difference (SMD) and dichotomous outcomes using relative risk (RR) (see supplement 1 - Methods).

The main body of the report presents only statistically significant and clinically important effects for the important (but not critical) outcomes (quality of life and functioning) and follow-up (of at least 6 months post-endpoint) of critical outcomes. Clinically important effects were defined using the default minimally important differences of a RR less than 0.8 or greater than 1.25 or a SMD less than -0.5 or greater than 0.5 or a logOR less than -0.25 or greater than 0.25 [MID for OR calculated as exp[0.52]=1.28]). However, forest plots for all outcomes and all time points are provided in supplements B2 and B3.

Similarly, in the main body of the report, comparisons between pairwise and NMA results for critical outcomes (base-case analysis) are restricted to highlighting comparisons where the difference between the pairwise meta-analysis and NMA results is equal to, or larger than, the minimally important difference (MID, as defined using the values given above). A distinction is also be made between differences where the effect estimate from the NMA is within the 95% confidence interval of the pairwise meta-analysis effect estimate, and differences where the effect estimate from the NMA is not within the 95% confidence interval of the pairwise meta-analysis as the latter (and not the former) may be considered a truly significant difference. The full table of pairwise meta-analysis and NMA comparisons is available in supplement B4. It is important to note that these comparisons have been performed in addition to the NMA inconsistency checks (where direct and indirect evidence is compared) as outlined above.

Evidence from pairwise meta-analyses for interventions that are only appropriate for subgroups of people with depression, specifically, couple interventions are presented in the relevant evidence sections below.

Subgroup analyses were only performed where the comparison and outcome had at least 2 studies in each subgroup. In the main body of the report, only subgroup analyses with statistically significant subgroup differences are presented (see appendix E for forest plots for all subgroup analyses).

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Less severe depression

Review question

For adults with a new episode of less severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Clinical evidence

Included studies

A total of 142 randomised controlled trials (RCTs) were included in this evidence review.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

The NMAs included 142 RCTs (k=142) representing 20,663 participants (n=20,663).

Of the 142 RCTs included in the NMAs for less severe depression, only 26 studies reported either a HAM-D or MADRS score at baseline, and for these studies the mean depression severity scores were HAM-D=12.99 (SD=7.66; k=23) and MADRS=17.74 (SD=6.87; k=3) respectively. Other commonly reported depression scales at baseline for RCTs within this network included the PHQ-9 (mean severity at baseline=12.78, SD=4.84, k=15), CES-D (mean severity at baseline=23.21, SD=9.30, k=35), BDI (mean severity at baseline=16.73, SD=6.89, k=16), and BDI-II (mean severity at baseline=22.38, SD=7.91, k=45). 10 studies were UK-based RCTs.

According to the interventions assessed and the types of outcomes reported in each RCT, the included RCTs have contributed data to one or more networks of evidence and respective NMAs.

For the SMD of depression symptom change scores outcome, the network of evidence (and the respective NMA) included 127 RCTs, 76 interventions grouped in 34 treatment classes, and 16,829 participants. Of the 127 RCTs, 10 reported change from baseline (CFB) depression symptom score data; 115 reported baseline and endpoint depression symptom score data; and 2 reported dichotomous response data and baseline symptom scores. These data were transformed and synthesised accordingly, allowing estimation of the SMD of depression symptom change scores (see appendix M for details).

For the outcome of response in those randomised, the network of evidence (and the respective NMA) included 75 RCTs, 53 interventions grouped in 26 treatment classes and 12,549 participants. Of the 75 RCTs, 11 reported dichotomous response data, 6 reported CFB depression symptom score data; and 58 reported baseline and endpoint depression symptom score data. These data were transformed and synthesised accordingly, allowing estimation of log-odds ratios of response (see appendix M for details).

For the outcome of remission in those randomised, the network of evidence (and the respective NMA) included 26 RCTs reporting dichotomous remission data, 25 interventions grouped in 16 treatment classes and 3,810 participants.

See the full evidence tables in appendix D.

Relevant information on the networks of evidence and the NMAs that informed the economic analysis are reported in appendix M.

Evidence from the network meta-analysis

Base-case analysis

Below is an overview of the treatment class network plots, numbers of people tested on each treatment class and intervention, and NMA findings at the treatment class level (relative effects versus the reference treatment and rankings), for every critical outcome considered in the clinical base-case analysis of treatments for adults with a new episode of less severe depression. For the outcome of the SMD of depressive symptom scores, relative effects of individual interventions versus the reference treatment are also provided in this section.

For each outcome, we present network plots, which depict all treatments considered in each analysis by nodes, and show which treatments have been directly compared in the RCTs included in each NMA, by connecting them with a direct line. In each network plot presented below, the width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.

Full results of the NMA, including network plots and relative effects of individual interventions, as well as relative effects of all pairs of treatment classes and individual interventions, are reported in appendix M and supplements B5 and B6.

SMD of depression symptom change scores

The network plot at the treatment class level is shown in Figure 1. The numbers of participants tested on each treatment class and each intervention are shown in The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.

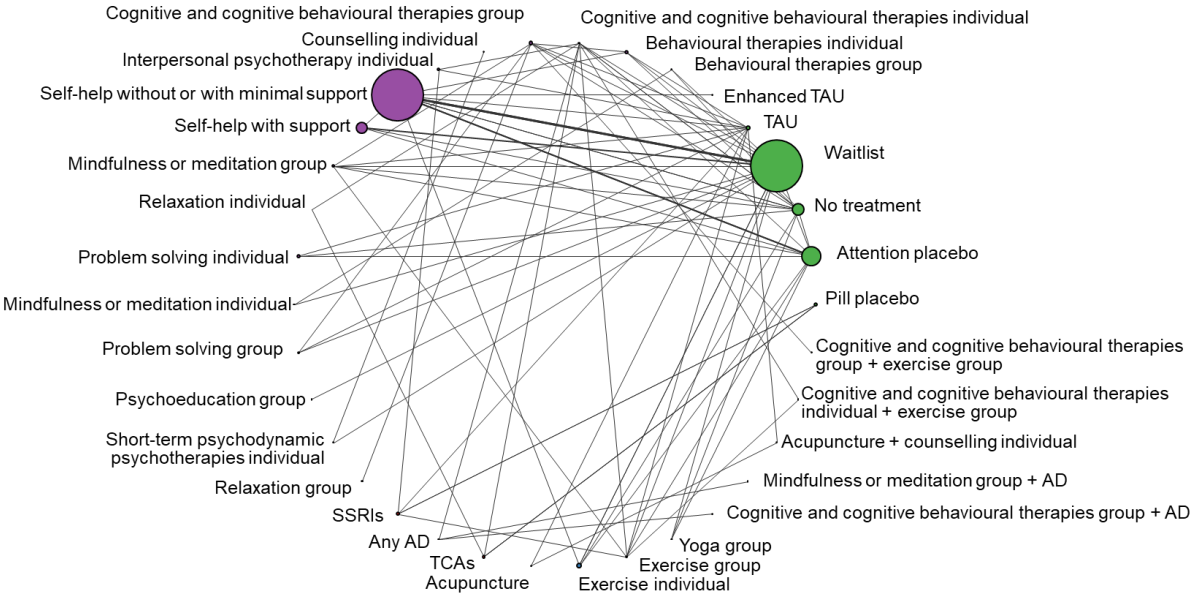
AD: antidepressant; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 2. The base-case relative effects (posterior mean SMD with 95% CrI) of all treatment classes versus TAU (reference treatment for less severe depression) are illustrated in

Figure 2 (forest plots) and reported in SSRIs: selective serotonin uptake inhibitors; TCAs: tricyclic antidepressants

Table 3. The same table also shows the class treatment rankings. Treatment classes in the table have been ordered from lowest to highest ranking (with lower rankings suggesting greater effects).

Figure 1. Network plot of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression – treatment class level



The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
AD: antidepressant; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 2. Treatment classes, interventions and numbers of participants tested on each in the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression

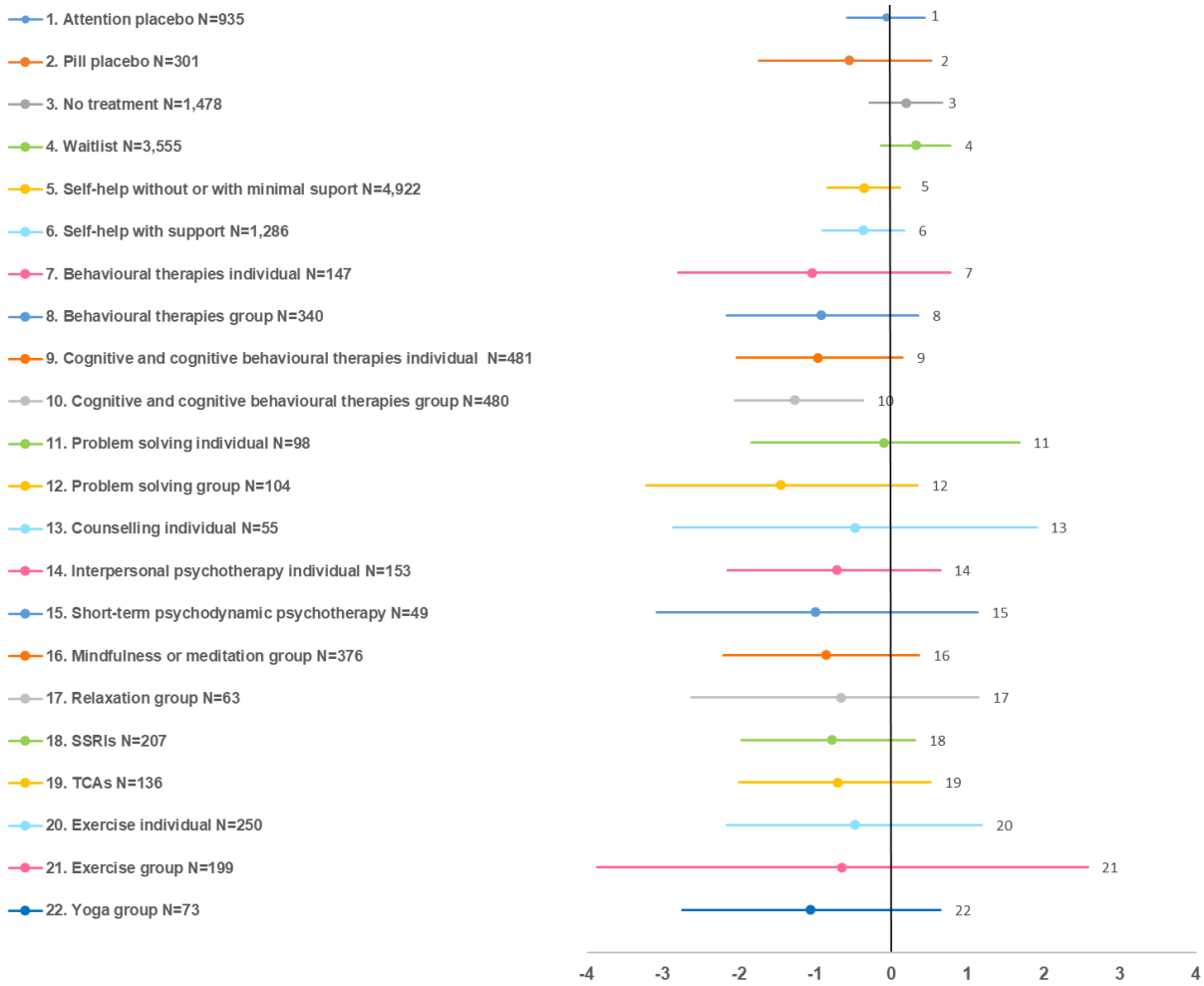
Treatment class	N	Intervention	N
Attention placebo	935	Attention placebo	935
Placebo	301	Pill placebo	301
No treatment	1,478	No treatment	1,478
Waitlist	3,555	Waitlist	3,555
TAU	815	TAU	815
Enhanced TAU	36	Enhanced TAU	36
Self-help without/with minimal support	4,922	Behavioural bibliotherapy	13
		Cognitive bibliotherapy	516
		Computerised-CBT (CCBT)	2,619
		Computerised attentional bias modification	230
		Computerised behavioural activation	122
		Computerised cognitive bias modification	75
		Computerised Coping with Depression course	257
		Computerised expressive writing	36
		Computerised mindfulness intervention	174
		Computerised positive psychological intervention	439
		Computerised problem solving therapy	232
		Computerised third-wave cognitive therapy	31
		Expressive writing	13
		Psychoeducational website	165

Self-help with support	1,286	Behavioural bibliotherapy with support	67
		Cognitive bias modification with support	20
		Cognitive bibliotherapy with support	125
		Computerised-CBT (CCBT) with support	396
		Computerised behavioural activation with support	40
		Computerised exercise promotion with support	24
		Computerised problem solving therapy with support	124
		Computerised third-wave cognitive therapy with support	82
		Expressive writing with support	125
		Third-wave cognitive therapy CD with support	283
Behavioural therapies individual	147	Behavioural activation (BA) individual	147
Behavioural therapies group	340	Behavioural activation (BA) group	117
		Coping with Depression course (group)	223
CT/CBT individual	481	CBT individual (15 sessions or over)	123
		CBT individual (under 15 sessions)	233
		Third-wave cognitive therapy individual	125
CT/CBT group	480	CBT group (15 sessions or over)	10
		CBT group (under 15 sessions)	316
		Positive psychotherapy (PPT) group	76
		Rational emotive behaviour therapy (REBT) group	14
		Third-wave cognitive therapy group	64
Problem solving individual	98	Problem solving individual	98
Problem solving group	104	Problem solving group	104
Counselling individual	55	Non-directive/supportive/person-centred counselling	55
IPT individual	153	Interpersonal counselling individual	17
		IPT individual	136
Short-term PDPT individual	49	Short-term PDPT individual	49
Psychoeducation group	22	Psychoeducational group programme	22
Mindfulness or meditation individual	20	Mindfulness-based stress reduction (MBSR) individual	20
Mindfulness or meditation group	376	Meditation-relaxation group	13
		Mindfulness-based cognitive therapy (MBCT) group	149
		Mindfulness-based stress reduction (MBSR) group	85
		Mindfulness meditation group	129
Relaxation individual	13	Progressive muscle relaxation individual	13
Relaxation group	63	Progressive muscle relaxation group	63
SSRIs	207	Any SSRI	24
		Citalopram	24
		Fluoxetine	78
		Sertraline	81
TCAs	136	Amitriptyline	67
		Any TCA	10
		Imipramine	36
		Lofepramine	23
Any AD	65	Any AD	65
Acupuncture	40	Traditional acupuncture	40
Exercise individual	250	Supervised high intensity exercise individual	43
		Supervised low intensity exercise individual	86
		Unsupervised low intensity exercise individual	121
Exercise group	199	Supervised high intensity exercise group	147
		Supervised low intensity exercise group	52
Yoga group	73	Yoga group	73

CT/CBT group + AD	32	CBT group (under 15 sessions) + any AD	32
Mindfulness or meditation group + AD	15	Body-mind-spirit group + any AD	15
Acupuncture + counselling individual	40	Traditional acupuncture + non-directive/supportive/person-centred counselling	40
CT/CBT individual + exercise group	18	CBT individual (under 15 sessions) + supervised high intensity exercise group	18
CT/CBT group + exercise group	25	CBT group (under 15 sessions) + supervised low intensity exercise group	25

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Figure 2. Base-case forest plots of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression: effects of treatment classes versus treatment as usual (TAU, N=815) Values on the left side of the vertical axis indicate better effect compared with TAU. Effects are shown only for treatment classes with N ≥ 50, plus short-term psychodynamic psychotherapy (N=49).



SSRIs: selective serotonin uptake inhibitors; TCAs: tricyclic antidepressants

Table 3. Base-case results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression: posterior effects (mean SMD, 95%CrI) of all treatment classes versus treatment as usual (TAU) and treatment class rankings

Treatment class	N	SMD vs TAU (mean, 95% CrI)	Rank (mean, 95% CrI)
CT/CBT group + exercise group	25	**-2.76 (-4.77 to -0.77)**	2.76 (1 to 14)
Problem solving group	104	-1.45 (-3.22 to 0.35)	8.65 (1 to 28)
CT/CBT group	480	**-1.27 (-2.05 to -0.38)**	8.92 (3 to 20)
Mindfulness or meditation group + AD	15	-1.54 (-4.17 to 1.07)	9.95 (1 to 31)
CT/CBT group + AD	32	-1.27 (-3.79 to 1.26)	11.87 (1 to 32)
Yoga group	73	-1.06 (-2.75 to 0.65)	12.18 (2 to 31)
Behavioural therapies individual	147	-1.04 (-2.80 to 0.77)	12.46 (2 to 30)
CT/CBT individual	481	-0.96 (-2.03 to 0.14)	12.64 (4 to 26)
Mindfulness or meditation individual	20	-1.03 (-3.04 to 1.01)	13.04 (2 to 31)
Behavioural therapies group	340	-0.92 (-2.16 to 0.36)	13.36 (3 to 28)
Short-term PDPT individual	49	-0.99 (-3.08 to 1.14)	13.50 (2 to 31)
Acupuncture + counselling individual	40	-0.94 (-2.84 to 0.95)	13.88 (2 to 31)
Mindfulness or meditation group	376	-0.85 (-2.20 to 0.36)	14.21 (3 to 29)
Acupuncture	40	-0.87 (-2.77 to 1.03)	14.67 (2 to 31)
Relaxation individual	13	-0.82 (-2.94 to 1.35)	15.28 (2 to 32)
SSRIs	207	-0.77 (-1.97 to 0.31)	15.35 (4 to 29)
IPT individual	153	-0.71 (-2.15 to 0.64)	16.21 (4 to 30)
TCAs	136	-0.70 (-2.00 to 0.52)	16.29 (4 to 30)
Exercise group	199	-0.65 (-3.86 to 2.58)	16.75 (1 to 32)
Relaxation group	63	-0.66 (-2.63 to 1.15)	16.99 (2 to 32)
Pill placebo	301	-0.55 (-1.74 to 0.53)	18.45 (5 to 30)
Counselling individual	55	-0.47 (-2.87 to 1.91)	18.70 (2 to 32)
Exercise individual	250	-0.48 (-2.16 to 1.18)	18.88 (3 to 32)
CT/CBT individual + exercise group	18	-0.39 (-2.40 to 1.67)	19.69 (3 to 32)
Self-help with support	1,286	-0.36 (-0.90 to 0.17)	20.82 (14 to 27)
Psychoeducation group	22	-0.27 (-2.26 to 1.77)	20.86 (3 to 32)
Self-help without/with minimal support	4,922	-0.36 (-0.84 to 0.11)	20.86 (15 to 26)
Problem solving individual	98	-0.10 (-1.83 to 1.68)	23.20 (5 to 32)
Attention placebo	935	-0.06 (-0.57 to 0.44)	25.24 (19 to 30)
TAU	815	Reference	25.95 (19 to 31)
Enhanced TAU	36	0.28 (-0.90 to 1.47)	27.20 (13 to 32)
Waitlist	3,555	0.32 (-0.13 to 0.78)	29.20 (25 to 32)

Treatment classes ordered from best to worst, according to mean ranking. Negative effect values indicate a favourable outcome for treatment classes compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

The base-case relative effects (posterior mean SMD with 95% CrI) of all individual interventions versus TAU (reference treatment for less severe depression) are reported in

Table 4. Interventions have been listed by treatment class.

Table 4. Base-case results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression: posterior effects (mean SMD, 95%CrI) of all interventions versus treatment as usual (TAU). Only interventions of interest belonging to classes with N ≥50 have been included in the table, plus short-term psychodynamic psychotherapy (N=49).

Treatment class	N	SMD vs TAU (mean, 95% CrI)	Intervention	N	SMD vs TAU (mean, 95% CrI)
Self-help without/with minimal support	4,922	-0.36 (-0.84 to 0.11)	Behavioural bibliotherapy	13	-0.37 (-0.93 to 0.16)
			Cognitive bibliotherapy	516	-0.33 (-0.81 to 0.16)
			Computerised-CBT (CCBT)	2,619	-0.33 (-0.82 to 0.16)
			Computerised attentional bias modification	230	-0.35 (-0.86 to 0.17)
			Computerised behavioural activation	122	-0.42 (-1.00 to 0.10)
			Computerised cognitive bias modification	75	-0.36 (-0.89 to 0.16)
			Computerised Coping with Depression course	257	-0.38 (-0.93 to 0.13)
			Computerised expressive writing	36	-0.36 (-0.91 to 0.19)
			Computerised mindfulness intervention	174	-0.35 (-0.87 to 0.17)
			Computerised positive psychological intervention	439	-0.33 (-0.83 to 0.19)
			Computerised problem solving therapy	232	-0.44 (-1.02 to 0.07)
			Computerised third-wave cognitive therapy	31	-0.38 (-0.95 to 0.15)
			Expressive writing	13	-0.40 (-1.00 to 0.14)
			Psychoeducational website	165	-0.36 (-0.91 to 0.16)
Self-help with support	1,286	-0.36 (-0.90 to 0.17)	Behavioural bibliotherapy + support	67	-0.32 (-0.94 to 0.33)
			Cognitive bias modification + support	20	-0.41 (-1.08 to 0.20)
			Cognitive bibliotherapy + support	125	-0.38 (-1.00 to 0.23)
			Computerised-CBT (CCBT) + support	396	-0.33 (-0.89 to 0.24)
			Computerised behavioural activation + support	40	-0.43 (-1.16 to 0.19)
			Computerised exercise promotion + support	24	-0.35 (-0.99 to 0.30)
			Computerised problem solving therapy + support	124	-0.33 (-0.92 to 0.29)
			Computerised third-wave CT with support	82	-0.36 (-1.00 to 0.26)

			Expressive writing with support	125	-0.31 (-0.9 to 0.30)
			Third-wave cognitive therapy CD with support	283	-0.37 (-1.00 to 0.25)
Behavioural therapies individual	147	-1.04 (-2.80 to 0.77)	**Behavioural activation (BA) individual**	**147**	**-1.04 (-1.82 to -0.27)**
Behavioural therapies group	340	-0.92 (-2.16 to 0.36)	**Behavioural activation (BA) group**	**117**	**-1.33 (-2.02 to -0.66)**
			Coping with Depression course (group)	223	-0.51 (-1.27 to 0.25)
Cognitive and cognitive behavioural therapies individual	481	-0.96 (-2.03 to 0.14)	**CBT individual (15 sessions or over)**	**123**	**-1.01 (-1.72 to -0.29)**
			CBT individual (under 15 sessions)	**233**	**-0.95 (-1.69 to -0.21)**
			Third-wave cognitive therapy individual	**125**	**-0.93 (-1.67 to -0.19)**
Cognitive and cognitive behavioural therapies group	**480**	**-1.27 (-2.05 to -0.38)**	CBT group (15 sessions or over)	10	-1.04 (-2.10 to 0.43)
			CBT group (under 15 sessions)	**316**	**-1.53 (-2.08 to -1.00)**
			Positive psychotherapy (PPT) group	**76**	**-1.07 (-1.70 to -0.35)**
			Rational emotive behaviour therapy (REBT) group	**14**	**-1.41 (-2.34 to -0.57)**
			Third-wave cognitive therapy group	**64**	**-1.31 (-2.01 to -0.60)**
Problem solving individual	98	-0.10 (-1.83 to 1.68)	Problem solving individual	98	-0.09 (-0.79 to 0.60)
Problem solving group	104	-1.45 (-3.22 to 0.35)	**Problem solving group**	104	**-1.46 (-2.25 to -0.65)**
Counselling individual	55	-0.47 (-2.87 to 1.91)	Non-directive/supportive/person-centred counselling	55	-0.44 (-2.22 to 1.37)
IPT individual	153	-0.71 (-2.15 to 0.64)	Interpersonal counselling individual	17	-0.78 (-2.14 to 0.46)
			IPT individual	**136**	**-0.64 (-1.28 to 0.00)**
Short-term PDPT individual	49	-0.99 (-3.08 to 1.14)	Short-term PDPT individual	49	-0.97 (-2.36 to 0.43)
Mindfulness or meditation group	376	-0.85 (-2.20 to 0.36)	**Meditation-relaxation group**	**13**	**-1.17 (-2.78 to 0.00)**
			MBCT group	**149**	**-0.83 (-1.43 to -0.23)**
			Mindfulness-based stress reduction (MBSR) group	85	-0.50 (-1.29 to 0.42)
			Mindfulness meditation group	**129**	**-0.93 (-1.75 to -0.17)**
Relaxation group	63	-0.66 (-2.63 to 1.15)	Progressive muscle relaxation group	63	-0.67 (-1.89 to 0.52)
SSRIs	207	-0.77 (-1.97 to 0.31)	Citalopram	24	-0.72 (-2.01 to 0.43)
			Fluoxetine	78	-0.85 (-2.25 to 0.28)
			Sertraline	81	-0.75 (-1.71 to 0.15)
TCAs	136	-0.70 (-2.00 to 0.52)	Amitriptyline	67	-0.93 (-2.51 to 0.34)
			Imipramine	36	-0.77 (-2.19 to 0.46)

			Lofepramine	23	-0.67 (-2.01 to 0.57)
Exercise individual	250	-0.48 (-2.16 to 1.18)	Supervised high intensity exercise individual	43	-0.62 (-1.39 to 0.12)
			Supervised low intensity exercise individual	86	-0.62 (-1.39 to 0.11)
			Unsupervised low intensity exercise individual	121	-0.23 (-1.01 to 0.60)
Exercise group	199	-0.65 (-3.86 to 2.58)	**Supervised high intensity exercise group**	**147**	**-0.74 (-1.44 to -0.06)**
			Supervised low intensity exercise group	52	-0.56 (-1.44 to 0.35)
Yoga group	73	-1.06 (-2.75 to 0.65)	**Yoga group**	**73**	**-1.06 (-1.92 to -0.22)**

Negative effect values indicate a favourable outcome for treatment classes and interventions compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.

CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Response in those randomised

The network plot at the treatment class level is shown in Figure 3. The number of participants tested on each treatment class and each intervention are shown in The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.

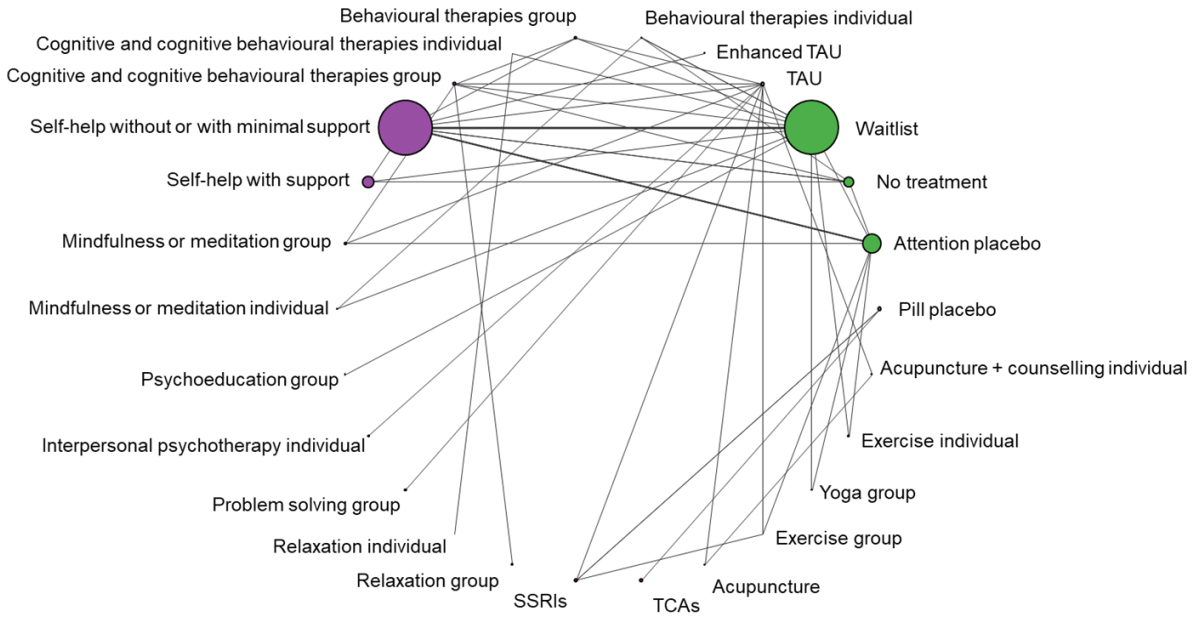
SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 5. The base-case relative effects (posterior mean log-odds ratio [LOR] with 95% CrI) of all treatment classes versus TAU (reference treatment for less severe depression) are illustrated in

Figure 4 (forest plots) and reported in

Table 6. The same table shows also the class treatment rankings. Treatment classes in the table have been ordered from lowest to highest ranking (with lower rankings suggesting greater effects).

Figure 3. Network plot of the NMA of response in those randomised in adults with a new episode of less severe depression – treatment class level



The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

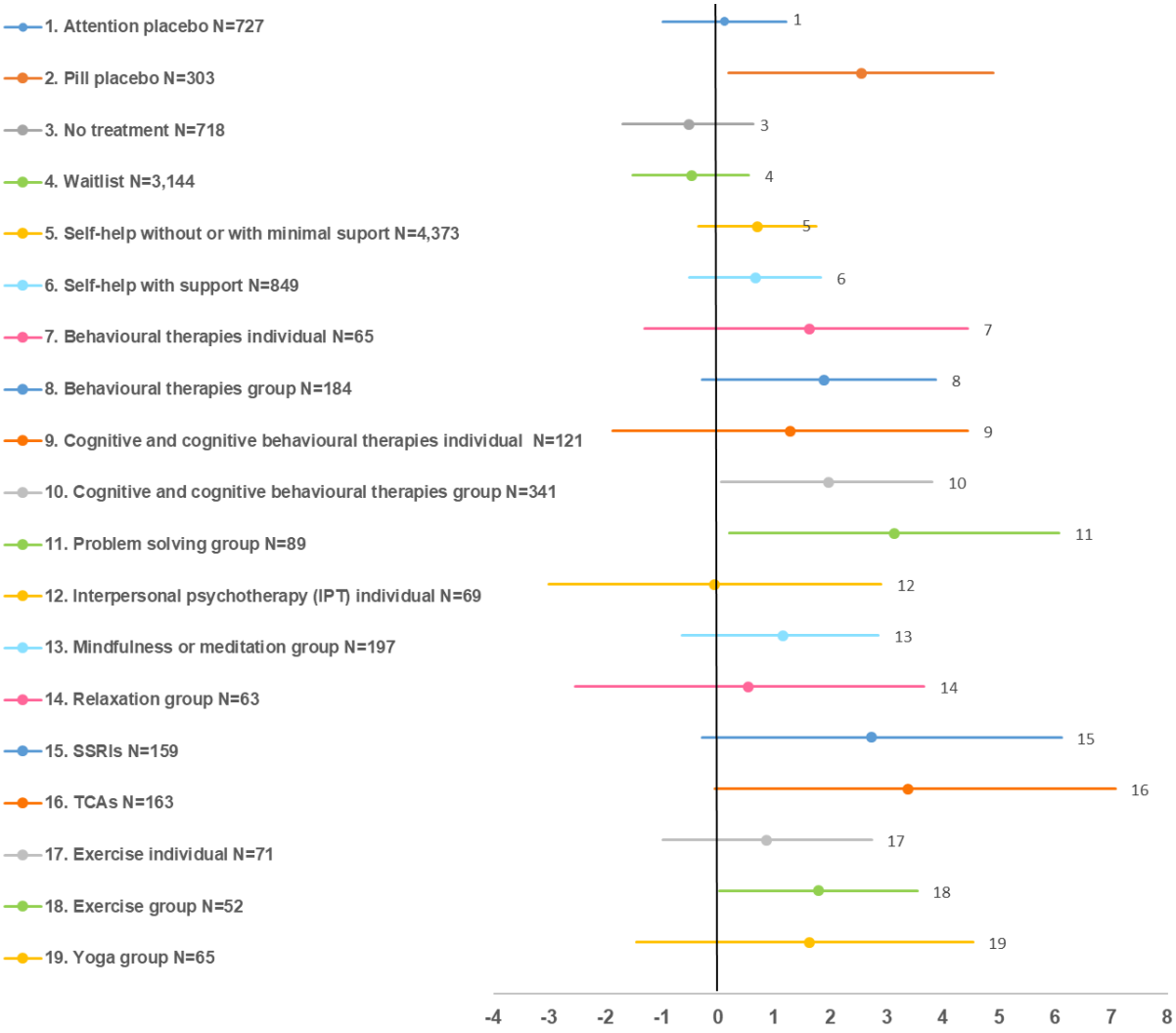
Table 5. Treatment classes, interventions and numbers of participants tested on each in the NMA of response in those randomised in adults with a new episode of less severe depression

Treatment class	N	Intervention	N
Waitlist	3,144	Waitlist	3,144
Placebo	303	Pill placebo	303
Attention placebo	727	Attention placebo	727
No treatment	718	No treatment	718
TAU	623	TAU	623
Enhanced TAU	36	Enhanced TAU	36
Self-help	4,373	Behavioural bibliotherapy	13
		Cognitive bibliotherapy	516
		Computerised-CBT (CCBT)	2,541
		Computerised attentional bias modification	181
		Computerised behavioural activation	10
		Computerised cognitive bias modification	55
		Computerised Coping with Depression course	190
		Computerised positive psychological intervention	439
		Computerised problem solving therapy	232
		Computerised third-wave cognitive therapy	31
		Psychoeducational website	165
Self-help with support	849	Behavioural bibliotherapy with support	67
		Cognitive bibliotherapy with support	125
		Computerised-CBT (CCBT) with support	262
		Computerised behavioural activation with support	40

		Computerised exercise promotion with support	24
		Computerised problem solving therapy with support	124
		Computerised third-wave cognitive therapy with support	82
		Expressive writing with support	125
Behavioural therapies individual	65	Behavioural activation (BA) individual	65
Behavioural therapies group	184	Behavioural activation (BA) group	85
		Coping with Depression course (group)	99
CT/CBT individual	121	CBT individual (15 sessions or over)	56
		Third-wave cognitive therapy individual	65
CT/CBT group	341	CBT group (15 sessions or over)	10
		CBT group (under 15 sessions)	267
		Third-wave cognitive therapy group	64
Problem solving group	89	Problem solving group	89
IPT individual	69	IPT individual	69
Psychoeducation group	22	Psychoeducational group programme	22
Mindfulness or meditation individual	20	Mindfulness-based stress reduction (MBSR) individual	20
Mindfulness or meditation group	197	Meditation-relaxation group	13
		Mindfulness-based cognitive therapy (MBCT) group	76
		Mindfulness-based stress reduction (MBSR) group	70
		Mindfulness meditation group	38
Relaxation individual	15	Progressive muscle relaxation individual	15
Relaxation group	63	Progressive muscle relaxation group	63
SSRIs	159	Fluoxetine	78
		Sertraline	81
TCAs	163	Amitriptyline	90
		Imipramine	73
Acupuncture	40	Traditional acupuncture	40
Exercise individual	71	Supervised low intensity exercise individual	71
Exercise group	52	Supervised high intensity exercise group	42
		Supervised low intensity exercise group	10
Yoga group	65	Yoga group	65
Acupuncture + counselling individual	40	Traditional acupuncture + non-directive/ supportive/ person-centred counselling	40

CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Figure 4. Forest plots of response in those randomised in adults with a new episode of less severe depression: effects of treatment classes versus treatment as usual (TAU, N=623) Values on the right side of the vertical axis indicate better effect compared with TAU. Results are expressed as log-odds ratios (LORs). Effects are shown only for treatment classes with N ≥ 50.



SSRIs: selective serotonin uptake inhibitors; TCAs: tricyclic antidepressants

Table 6. Base-case results of the NMA of response in those randomised in adults with a new episode of less severe depression: posterior effects (mean log-odds ratio [LOR], 95%CrI) of all treatment classes versus treatment as usual (TAU) and treatment class rankings

Treatment class	N	LOR vs TAU (mean, 95% CrI)	Rank (mean, 95% CrI)
TCAs	163	3.37 (-0.05 to 7.07)	4.54 (1 to 20)
Problem solving group	89	**3.14 (0.21 to 6.07)**	4.86 (1 to 18)
SSRIs	159	2.74 (-0.27 to 6.11)	6.27 (1 to 21)
Pill placebo	303	**2.55 (0.19 to 4.90)**	6.75 (2 to 19)
CT/CBT group	341	**1.96 (0.06 to 3.81)**	8.32 (2 to 18)
Behavioural therapies group	184	1.88 (-0.29 to 3.88)	8.86 (2 to 20)
Exercise group	52	**1.79 (0.02 to 3.54)**	9.27 (2 to 20)
Acupuncture + counselling individual	40	1.70 (-1.26 to 4.69)	10.30 (1 to 24)
Behavioural therapies individual	65	1.63 (-1.30 to 4.44)	10.40 (1 to 23)
Yoga group	65	1.63 (-1.45 to 4.54)	10.51 (1 to 24)
Acupuncture	40	1.59 (-1.39 to 4.60)	10.81 (1 to 24)
Mindfulness or meditation individual	20	1.56 (-1.75 to 4.74)	11.06 (1 to 24)
CT/CBT individual	121	1.29 (-1.87 to 4.44)	12.16 (1 to 24)
Mindfulness or meditation group	197	1.15 (-0.64 to 2.85)	12.76 (4 to 22)
Exercise individual	71	0.87 (-0.97 to 2.73)	14.24 (5 to 23)
Self-help without/with minimal support	4,373	0.71 (-0.35 to 1.75)	15.23 (10 to 19)
Psychoeducation group	22	0.61 (-2.71 to 3.81)	15.36 (2 to 25)
Self-help with support	849	0.66 (-0.52 to 1.83)	15.62 (10 to 21)
Relaxation group	63	0.55 (-2.54 to 3.67)	15.91 (2 to 25)
IPT individual	69	-0.06 (-3.01 to 2.90)	18.48 (4 to 25)
Attention placebo	727	0.13 (-0.98 to 1.21)	19.07 (14 to 23)
TAU	623	Reference	19.61 (14 to 24)
Enhanced TAU	36	-0.49 (-2.56 to 1.59)	20.98 (11 to 25)
Relaxation individual	15	-2.30 (-9.68 to 3.16)	21.53 (4 to 25)
Waitlist	3,144	-0.47 (-1.51 to 0.55)	22.09 (18 to 25)

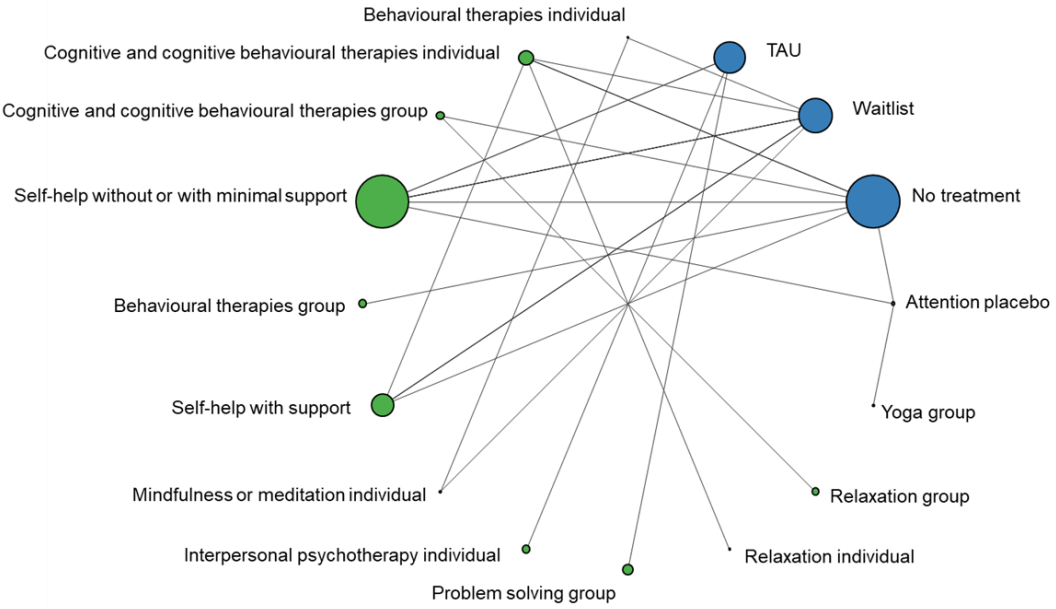
Treatment classes ordered from best to worst, according to mean ranking. Positive effect values indicate a favourable outcome for treatment classes compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.
CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; LOR: log-odds ratio; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Remission in those randomised

The network plot at the treatment class level is shown in Figure 5. The number of participants tested on each treatment class and each intervention are shown in The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
TAU: treatment as usual

Table 7. The base-case relative effects (posterior mean log-odds ratio [LOR] with 95% CrI) of all treatment classes versus TAU (reference treatment for less severe depression) are illustrated in Figure 6 (forest plots) and reported in Table 8. The same table shows also the class treatment rankings. Treatment classes in the table have been ordered from lowest to highest ranking (with lower rankings suggesting greater effects).

Figure 5. Network plot of the NMA of remission in those randomised in adults with a new episode of less severe depression – treatment class level



The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
TAU: treatment as usual

Table 7. Treatment classes, interventions and numbers of participants tested on each in the NMA of remission in those randomised in adults with a new episode of less severe depression

Treatment class	N	Intervention	N
No treatment	751	No treatment	751
Attention placebo	46	Attention placebo	46
Waitlist	468	Waitlist	468
TAU	437	TAU	437
Self-help without/with minimal support	1,050	Cognitive bibliotherapy	287
		Computerised-CBT (CCBT)	559
		Computerised attentional bias modification	28
		Computerised Coping with Depression course	88
		Computerised problem solving therapy	88
Self-help with support	348	Computerised-CBT (CCBT) with support	184
		Computerised behavioural activation with support	40
		Computerised problem solving therapy with support	124
Behavioural therapies individual	16	Behavioural activation (BA) individual	16
Behavioural therapies group	68	Coping with Depression course (group)	68
CT/CBT individual	233	CBT individual (15 sessions or over)	12
		CBT individual (under 15 sessions)	116
		Third-wave cognitive therapy individual	105
CT/CBT group	117	CBT group (15 sessions or over)	47
		CBT group (under 15 sessions)	70
Problem solving group	89	Problem solving group	89
IPT individual	69	IPT individual	69
Mindfulness or meditation individual	20	Mindfulness-based stress reduction (MBSR) individual	20
Relaxation individual	15	Progressive muscle relaxation individual	15
Relaxation group	63	Progressive muscle relaxation group	63
Yoga group	20	Yoga group	20

CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; TAU: treatment as usual

Figure 6. Forest plots of remission in those randomised in adults with a new episode of less severe depression: effects of treatment classes versus treatment as usual (TAU, N=437) Values on the right side of the vertical axis indicate better effect compared with TAU. Only classes with N ≥ 50 are shown.

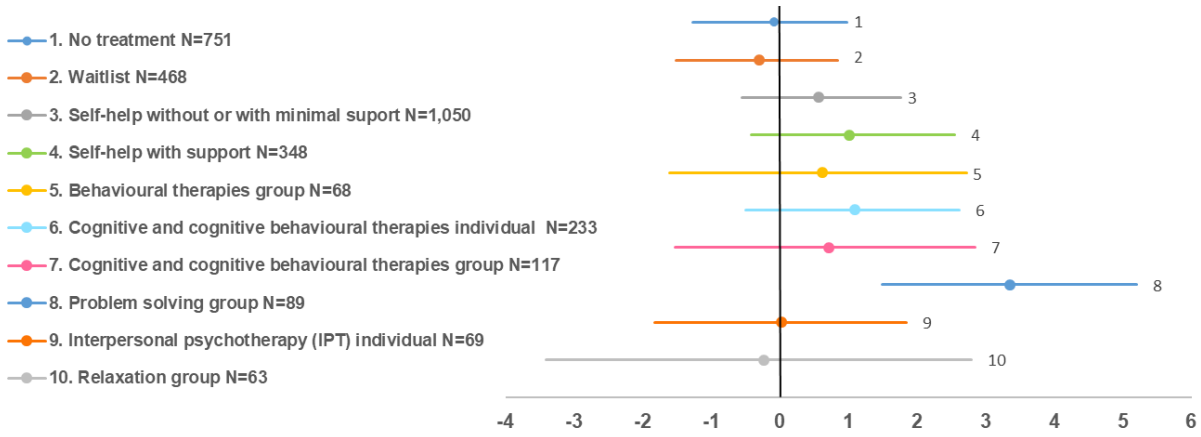


Table 8. Base-case results of the NMA of remission in those randomised in adults with a new episode of less severe depression: posterior effects (mean log-odds ratio [LOR], 95%CrI) of all treatment classes versus treatment as usual (TAU) and treatment class rankings

Treatment class	N	LOR vs TAU (mean, 95% CrI)	Rank (mean, 95% CrI)
Problem solving group	89	**3.36 (1.50 to 5.20)**	1.59 (1 to 5)
Yoga group	20	2.02 (-2.04 to 6.54)	4.58 (1 to 14)
CT/CBT individual	233	1.09 (-0.49 to 2.62)	5.38 (2 to 11)
Behavioural therapies individual	16	1.25 (-1.35 to 3.95)	5.45 (1 to 13)
Self-help with support	348	1.01 (-0.42 to 2.55)	5.72 (2 to 10)
Mindfulness or meditation individual	20	0.91 (-1.65 to 3.53)	6.57 (2 to 14)
CT/CBT group	117	0.72 (-1.53 to 2.85)	7.02 (2 to 13)
Behavioural therapies group	68	0.62 (-1.60 to 2.73)	7.49 (2 to 14)
Self-help without/with minimal support	1,050	0.56 (-0.55 to 1.77)	7.74 (4 to 11)
IPT individual	69	0.02 (-1.82 to 1.84)	9.81 (3 to 15)
TAU	437	Reference	10.27 (5 to 14)
Relaxation group	63	-0.23 (-3.41 to 2.79)	10.48 (2 to 15)
Waitlist	468	-0.3 (-1.51 to 0.84)	11.60 (8 to 14)
Attention placebo	46	-1.14 (-4.11 to 1.59)	12.67 (5 to 15)
Relaxation individual	15	-3.08 (-10.48 to 1.51)	13.64 (5 to 15)

Treatment classes ordered from best to worst, according to mean ranking. Positive effect values indicate a favourable outcome for treatment classes compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.
CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; LOR; log-odds ratios

Bias-adjusted analysis

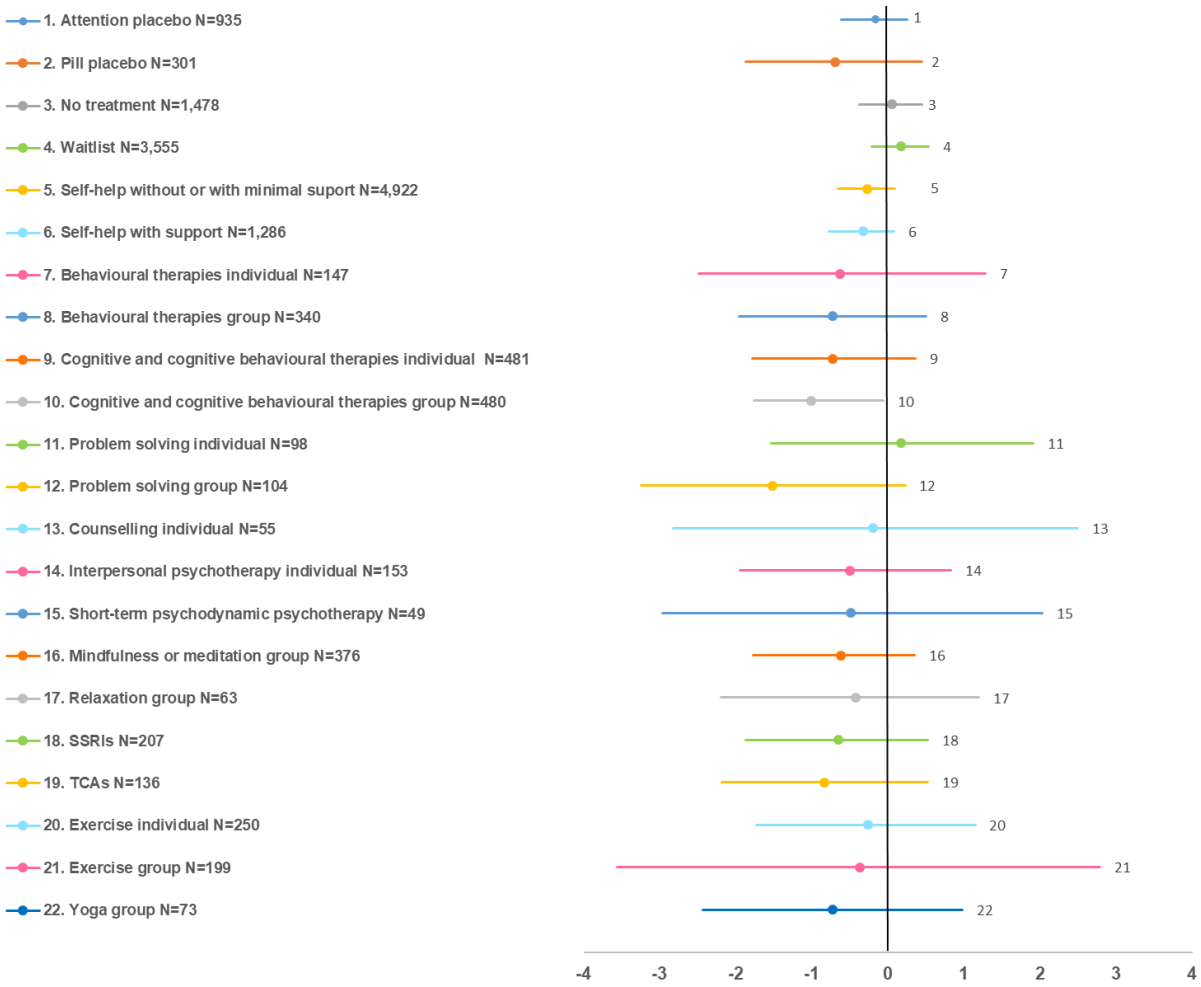
Bias models tested on the SMD outcome suggested evidence of bias due to small study size.

Figure 7 shows the bias-adjusted forest plots of relative effects (posterior mean SMD with 95% CrI) of all treatment classes versus TAU (reference treatment for less severe depression). Table 9 shows the relative effects of all treatment

classes versus TAU on the SMD and the class treatment rankings. Treatment classes in the table have been ranked from lowest to highest ranking (with lower rankings suggesting greater effects).

Table 10 shows the bias-adjusted relative effects (posterior mean SMD with 95% CrI) of all individual interventions versus TAU (reference treatment for less severe depression). Interventions in this table have been listed by treatment class.

Figure 7. Bias-adjusted forest plots of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression: effects of treatment classes versus treatment as usual (TAU, N=815). Values on the left side of the vertical axis indicate better effect compared with TAU. Effects are shown only for treatment classes with N ≥ 50, plus short-term psychodynamic psychotherapy (N=49).



SSRIs: selective serotonin uptake inhibitors; TCAs: tricyclic antidepressants

Table 9. Bias-adjusted results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression: posterior effects (mean SMD, 95%CrI) of all treatment classes versus treatment as usual (TAU) and treatment class rankings

Treatment class	N	SMD vs TAU (mean, 95% CrI)	Rank (mean, 95% CrI)
CT/CBT group + exercise group	25	**-2.51 (-4.42 to -0.61)**	2.92 (1 to 14)
Problem solving group	104	-1.52 (-3.24 to 0.23)	6.61 (1 to 26)
CT/CBT group	480	**-1.01 (-1.76 to -0.06)**	9.55 (3 to 22)
Mindfulness or meditation group + AD	15	-1.23 (-5.14 to 2.80)	12.22 (1 to 32)
Behavioural therapies group	340	-0.73 (-1.95 to 0.50)	13.09 (3 to 28)
CT/CBT individual	481	-0.73 (-1.78 to 0.36)	13.14 (4 to 27)
TCAs	136	-0.83 (-2.18 to 0.53)	13.27 (3 to 29)
CT/CBT group + AD	32	-1.00 (-4.47 to 2.61)	13.34 (1 to 32)
Acupuncture + counselling individual	40	-0.78 (-2.57 to 1.02)	13.37 (2 to 31)
Yoga group	73	-0.73 (-2.43 to 0.98)	13.83 (2 to 31)
Acupuncture	40	-0.69 (-2.50 to 1.13)	14.26 (2 to 31)
Mindfulness or meditation group	376	-0.62 (-1.77 to 0.35)	14.47 (4 to 28)
Behavioural therapies individual	147	-0.63 (-2.48 to 1.28)	14.72 (2 to 31)
Pill placebo	301	-0.69 (-1.87 to 0.45)	15.09 (4 to 29)
SSRIs	207	-0.64 (-1.87 to 0.53)	15.90 (4 to 30)
Mindfulness or meditation individual	20	-0.52 (-3.10 to 2.22)	16.09 (1 to 32)
Short-term PDPT individual	49	-0.48 (-2.96 to 2.03)	16.49 (2 to 32)
IPT individual	153	-0.5 (-1.94 to 0.83)	16.93 (4 to 30)
Relaxation group	63	-0.42 (-2.19 to 1.20)	17.84 (3 to 32)
Exercise group	199	-0.37 (-3.56 to 2.79)	17.91 (1 to 32)
Self-help with support	1,286	-0.33 (-0.77 to 0.08)	18.22 (11 to 25)
Relaxation individual	13	-0.41 (-3.07 to 2.23)	18.39 (1 to 32)
Counselling individual	55	-0.20 (-2.82 to 2.5)	19.20 (2 to 32)
Exercise individual	250	-0.26 (-1.73 to 1.15)	19.43 (4 to 31)
Self-help without/with minimal support	4,922	-0.27 (-0.66 to 0.09)	19.51 (13 to 25)
CT/CBT individual + exercise group	18	-0.18 (-2.75 to 2.44)	19.78 (2 to 32)
Psychoeducation group	22	-0.09 (-2.07 to 1.96)	20.80 (3 to 32)
Attention placebo	935	-0.16 (-0.61 to 0.25)	21.52 (14 to 28)
Problem solving individual	98	0.17 (-1.53 to 1.91)	24.28 (6 to 32)
TAU	815	Reference	24.35 (18 to 30)
Enhanced TAU	36	0.16 (-0.81 to 1.13)	24.90 (11 to 32)
Waitlist	3,555	0.17 (-0.21 to 0.54)	26.56 (21 to 31)

Treatment classes ordered from best to worst, according to mean ranking. Negative effect values indicate a favourable outcome for treatment classes compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 10. Bias-adjusted results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of less severe depression: posterior effects (mean SMD, 95%CrI) of all interventions versus treatment as usual (TAU). Only interventions of interest belonging to classes with N ≥50 have been included in the table, plus short-term psychodynamic psychotherapy.

Treatment class	N	SMD vs TAU (mean, 95% CrI)	Intervention	N	SMD vs TAU (mean, 95% CrI)
Self-help without or with minimal support	4,922	-0.27 (-0.66 to 0.09)	Behavioural bibliotherapy	13	-0.27 (-0.69 to 0.13)
			Cognitive bibliotherapy	516	-0.27 (-0.64 to 0.08)
			Computerised-CBT (CCBT)	2,619	-0.26 (-0.64 to 0.10)
			Computerised attentional bias modification	230	-0.25 (-0.65 to 0.14)
			Computerised behavioural activation	122	-0.31 (-0.75 to 0.07)
			Computerised cognitive bias modification	75	-0.27 (-0.68 to 0.13)
			Computerised Coping with Depression course	257	-0.28 (-0.69 to 0.09)
			Computerised expressive writing	36	-0.27 (-0.68 to 0.13)
			Computerised mindfulness intervention	174	-0.26 (-0.67 to 0.12)
			Computerised positive psychological intervention	439	-0.26 (-0.65 to 0.12)
			Computerised problem solving therapy	232	-0.29 (-0.71 to 0.08)
			Computerised third-wave cognitive therapy	31	-0.27 (-0.70 to 0.12)
			Expressive writing	13	-0.27 (-0.69 to 0.12)
			Psychoeducational website	165	-0.28 (-0.69 to 0.10)
Self-help with support	1,286	-0.33 (-0.77 to 0.08)	Behavioural bibliotherapy + support	67	-0.30 (-0.79 to 0.22)
			Cognitive bias modification + support	20	-0.36 (-0.91 to 0.13)
			Cognitive bibliotherapy + support	125	-0.38 (-0.86 to 0.07)
			Computerised-CBT (CCBT) + support	396	-0.30 (-0.74 to 0.12)
			Computerised behavioural activation + support	40	-0.39 (-0.97 to 0.11)
			Computerised exercise promotion + support	24	-0.32 (-0.84 to 0.21)
			Computerised problem solving therapy + support	124	-0.32 (-0.78 to 0.14)

			Computerised third-wave CT with support	82	-0.35 (-0.84 to 0.11)
			Expressive writing with support	125	-0.29 (-0.75 to 0.19)
			Third-wave cognitive therapy CD with support	283	-0.40 (-0.90 to 0.06)
Behavioural therapies individual	147	-0.63 (-2.48 to 1.28)	Behavioural activation (BA) individual	147	-0.63 (-1.63 to 0.45)
Behavioural therapies group	340	-0.73 (-1.95 to 0.50)	**Behavioural activation (BA) group**	**117**	**-1.10 (-1.69 to -0.53)**
			Coping with Depression course (group)	223	-0.33 (-0.93 to 0.23)
CT/CBT individual	481	-0.73 (-1.78 to 0.36)	CBT individual (15 sessions or over)	123	-0.68 (-1.36 to 0.01)
			CBT individual (under 15 sessions)	233	-0.66 (-1.45 to 0.16)
			Third-wave cognitive therapy individual	**125**	**-0.75 (-1.42 to -0.10)**
CT/CBT group	**480**	**-1.01 (-1.76 to -0.06)**	CBT group (15 sessions or over)	10	-0.84 (-1.91 to 0.78)
			CBT group (under 15 sessions)	**316**	**-1.25 (-1.72 to -0.83)**
			Positive psychotherapy (PPT) group	**76**	**-0.92 (-1.48 to -0.27)**
			Rational emotive behaviour therapy (REBT) group	14	-1.02 (-2.13 to 0.18)
			Third-wave cognitive therapy group	**64**	**-0.93 (-1.59 to -0.17)**
Problem solving individual	98	0.17 (-1.53 to 1.91)	Problem solving individual	98	0.18 (-0.46 to 0.81)
Problem solving group	104	-1.52 (-3.24 to 0.23)	**Problem solving group**	**104**	**-1.53 (-2.15 to -0.89)**
Counselling individual	55	-0.20 (-2.82 to 2.50)	Non-directive/supportive/person-centred counselling	55	-0.20 (-2.52 to 2.06)
IPT individual	153	-0.50 (-1.94 to 0.83)	Interpersonal counselling individual	17	-0.57 (-2.03 to 0.66)
			IPT individual	136	-0.37 (-0.90 to 0.14)
Short-term PDPT individual	49	-0.48 (-2.96 to 2.03)	Short-term PDPT individual	49	-0.48 (-2.58 to 1.59)
Mindfulness or meditation group	376	-0.62 (-1.77 to 0.35)	Meditation-relaxation group	13	-0.75 (-2.46 to 0.39)
			MBCT group	**149**	**-0.59 (-1.11 to -0.10)**
			Mindfulness-based stress reduction (MBSR) group	85	-0.37 (-1.01 to 0.32)
			Mindfulness meditation group	**129**	**-0.65 (-1.39 to -0.01)**
Relaxation group	63	-0.42 (-2.19 to 1.20)	Progressive muscle relaxation group	63	-0.39 (-1.33 to 0.53)
SSRIs	207	-0.64 (-1.87 to 0.53)	Citalopram	24	-0.54 (-1.92 to 0.72)
			Fluoxetine	78	-0.73 (-2.21 to 0.52)
			Sertraline	81	-0.52 (-1.70 to 0.59)
TCAs	136	-0.83 (-2.18 to 0.53)	Amitriptyline	67	-1.03 (-2.55 to 0.29)

			Imipramine	36	-0.80 (-2.29 to 0.52)
			Lofepramine	23	-0.69 (-2.15 to 0.65)
Exercise individual	250	-0.26 (-1.73 to 1.15)	Supervised high intensity exercise individual	43	-0.42 (-1.32 to 0.34)
			Supervised low intensity exercise individual	86	-0.24 (-0.89 to 0.39)
			Unsupervised low intensity exercise individual	121	-0.13 (-0.76 to 0.51)
Exercise group	199	-0.37 (-3.56 to 2.79)	Supervised high intensity exercise group	147	-0.25 (-1.03 to 0.53)
			Supervised low intensity exercise group	52	-0.45 (-1.23 to 0.32)
Yoga group	73	-0.73 (-2.43 to 0.98)	Yoga group	73	-0.72 (-1.70 to 0.28)

Negative effect values indicate a favourable outcome for treatment classes and interventions compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.

CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Sensitivity analyses

Effects on the SMD of all treatment classes versus TAU in the post-hoc sensitivity analysis that included only RCTs rated as being at low risk of bias for attrition in the Cochrane Risk of Bias tool are presented in Table 11, alongside the base-case analysis effects, to allow comparison between the two sets of results.

Table 11. Comparison of results following inclusion only of trials at low risk of bias for attrition in the NMA and results of the NMA base-case analysis: standardised mean difference (SMD) of depression symptom scores in adults with a new episode of less severe depression

Low risk of bias for attrition dataset			Full dataset – base-case analysis		
Treatment class	**N**	**Effect vs TAU (mean SMD, 95%CrI)**	**Treatment class**	**N**	**Effect vs TAU (mean SMD, 95%CrI)**
CT/CBT group	395	**-1.41 (-2.18 to -0.59)**	CT/CBT group + exercise group	25	**-2.76 (-4.77 to -0.77)**
Problem solving group	104	-1.41 (-4.00 to 1.23)	Problem solving group	104	-1.45 (-3.22 to 0.35)
TCAs	103	-1.54 (-6.22 to 3.14)	CT/CBT group	480	**-1.27 (-2.05 to -0.38)**
SSRIs	113	-1.20 (-4.48 to 2.12)	Mindfulness or meditation group + AD	15	-1.54 (-4.17 to 1.07)
Mindfulness or meditation group + AD	15	-1.24 (-4.63 to 2.12)	CT/CBT group + AD	32	-1.27 (-3.79 to 1.26)
Yoga group	73	-0.90 (-2.35 to 0.57)	Yoga group	73	-1.06 (-2.75 to 0.65)
Behavioural therapies group	216	-0.88 (-2.64 to 1.15)	Behavioural therapies individual	147	-1.04 (-2.80 to 0.77)
Acupuncture + counselling individual	40	-0.94 (-3.65 to 1.73)	CT/CBT individual	481	-0.96 (-2.03 to 0.14)
Behavioural therapies individual	46	-0.86 (-3.49 to 1.83)	Mindfulness or meditation individual	20	-1.03 (-3.04 to 1.01)
CT/CBT group + AD	32	-0.97 (-4.28 to 2.35)	Behavioural therapies group	340	-0.92 (-2.16 to 0.36)
Acupuncture	40	-0.88 (-3.59 to 1.85)	Short-term PDPT individual	49	-0.99 (-3.08 to 1.14)
Mindfulness or meditation individual	20	-0.86 (-3.66 to 1.98)	Acupuncture + counselling individual	40	-0.94 (-2.84 to 0.95)
Mindfulness or meditation group	318	-0.74 (-1.68 to 0.26)	Mindfulness or meditation group	376	-0.85 (-2.20 to 0.36)
Relaxation group	63	-0.77 (-2.61 to 0.96)	Acupuncture	40	-0.87 (-2.77 to 1.03)
Exercise group	136	-0.71 (-1.80 to 0.35)	Relaxation individual	13	-0.82 (-2.94 to 1.35)
CT/CBT individual	336	-0.68 (-2.27 to 0.95)	SSRIs	207	-0.77 (-1.97 to 0.31)
IPT individual	103	-0.49 (-3.10 to 2.08)	IPT individual	153	-0.71 (-2.15 to 0.64)

CT/CBT group + exercise group	18	-0.24 (-3.05 to 2.63)	TCAs	136	-0.70 (-2.00 to 0.52)
Self-help without/with minimal support	1,743	-0.32 (-1.00 to 0.34)	Exercise group	199	-0.65 (-3.86 to 2.58)
Psychoeducation group	22	-0.13 (-2.91 to 2.73)	Relaxation group	63	-0.66 (-2.63 to 1.15)
Self-help with support	958	-0.21 (-0.96 to 0.54)	Counselling individual	55	-0.47 (-2.87 to 1.91)
Exercise individual	85	-0.12 (-1.20 to 0.97)	Exercise individual	250	-0.48 (-2.16 to 1.18)
			CT/CBT individual + exercise group	18	-0.39 (-2.40 to 1.67)
			Self-help with support	1,286	-0.36 (-0.90 to 0.17)
			Psychoeducation group	22	-0.27 (-2.26 to 1.77)
			Self-help without/with minimal support	4,922	-0.36 (-0.84 to 0.11)
			Problem solving individual	98	-0.10 (-1.83 to 1.68)

Treatment classes ordered from best to worst, according to mean ranking in each analysis. Negative effect values indicate a favourable outcome for treatment classes compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.
No RCTs at low risk of bias for attrition were identified for counselling individual, short-term psychodynamic psychotherapy, combined CT/CBT individual and exercise, relaxarion individual, and problem solving individual; therefore these treatment classes were not included in the respective sensitivity analysis.
CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; TAU: treatment as usual

Finally, effects on the SMD of all treatment classes versus TAU in the sensitivity analysis conducted after excluding pharmacological trials are reported in Table 12, presented alongside the base-case analysis effects, to allow comparison between the two sets of results. In each analysis, treatment classes have been ordered from lowest to highest ranking (with lower rankings suggesting higher effects).

Table 12. Comparison of results following exclusion of pharmacological trials from the NMA and results of the NMA base-case analysis: standardised mean difference (SMD) of depression symptom scores in adults with a new episode of less severe depression

Non-pharmacological dataset			Full dataset – base-case analysis		
Treatment class	**N**	**Effect vs TAU (mean SMD, 95%CrI)**	**Treatment class**	**N**	**Effect vs TAU (mean SMD, 95%CrI)**
CT/CBT group + exercise group	25	**-2.72 (-5.26 to -0.24)**	CT/CBT group + exercise group	25	**-2.76 (-4.77 to -0.77)**
CT/CBT group	480	**-1.22 (-2.03 to -0.30)**	Problem solving group	104	-1.45 (-3.22 to 0.35)
Problem solving group	104	-1.43 (-3.81 to 0.93)	CT/CBT group	480	**-1.27 (-2.05 to -0.38)**
Yoga group	73	-0.97 (-2.70 to 0.76)	Yoga group	73	-1.06 (-2.75 to 0.65)
Behavioural therapies individual	147	-0.97 (-3.30 to 1.41)	Behavioural therapies individual	147	-1.04 (-2.80 to 0.77)
Mindfulness or meditation individual	20	-0.97 (-3.45 to 1.56)	CT/CBT individual	481	-0.96 (-2.03 to 0.14)
Behavioural therapies group	340	-0.86 (-2.51 to 0.82)	Mindfulness or meditation individual	20	-1.03 (-3.04 to 1.01)

Acupuncture + counselling individual	40	-0.93 (-3.35 to 1.45)	Behavioural therapies group	340	-0.92 (-2.16 to 0.36)
Short-term PDPT individual	49	-0.91 (-3.48 to 1.63)	Short-term PDPT individual	49	-0.99 (-3.08 to 1.14)
CT/CBT individual	450	-0.79 (-2.17 to 0.64)	Acupuncture + counselling individual	40	-0.94 (-2.84 to 0.95)
Mindfulness or meditation group	376	-0.78 (-2.11 to 0.42)	Mindfulness or meditation group	376	-0.85 (-2.20 to 0.36)
Acupuncture	40	-0.87 (-3.32 to 1.57)	Acupuncture	40	-0.87 (-2.77 to 1.03)
Relaxation group	63	-0.63 (-2.59 to 1.21)	IPT individual	153	-0.71 (-2.15 to 0.64)
Exercise group	185	-0.56 (-1.38 to 0.26)	Exercise group	199	-0.65 (-3.86 to 2.58)
IPT individual	136	-0.53 (-2.82 to 1.82)	Relaxation group	63	-0.66 (-2.63 to 1.15)
Exercise individual	250	-0.40 (-1.06 to 0.24)	Counselling individual	55	-0.47 (-2.87 to 1.91)
Counselling individual	55	-0.39 (-3.16 to 2.42)	Exercise individual	250	-0.48 (-2.16 to 1.18)
CT/CBT individual + exercise group	18	-0.24 (-2.77 to 2.30)	CT/CBT individual + exercise group	18	-0.39 (-2.40 to 1.67)
Self-help without/with minimal support	4,922	-0.30 (-0.79 to 0.19)	Self-help with support	1,286	-0.36 (-0.90 to 0.17)
Psychoeducation group	22	-0.21 (-2.72 to 2.29)	Psychoeducation group	22	-0.27 (-2.26 to 1.77)
Self-help with support	1,286	-0.28 (-0.82 to 0.26)	Self-help without/with minimal support	4,922	-0.36 (-0.84 to 0.11)
Problem solving individual	98	-0.06 (-2.36 to 2.28)	Problem solving individual	98	-0.10 (-1.83 to 1.68)

Treatment classes ordered from best to worst, according to mean ranking in each analysis. Negative effect values indicate a favourable outcome for treatment classes compared with TAU. Results where 95% CrI do not cross the no effect line are shown in bold.
CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; TAU: treatment as usual

Evidence from the pairwise meta-analyses

Important (but not critical) outcomes

See Table 13 for a summary of the clinically important and statistically significant effects observed for the important (but not critical) outcomes of quality of life and functioning (including personal, social, and occupational functioning and global functioning/functional impairment) at endpoint and longer-term (at least 6 months) follow-up. See supplement B2 for forest plots for all important (but not critical) outcomes.

Table 13. Summary of significant important (but not critical outcomes) at endpoint and longer-term (at least 6 months) follow-up for adults with a new episode of less severe depression

Intervention	Control	Outcome	Participants (N); Studies (K)	Effect estimate (95% CI)
Behavioural individual	No treatment	Quality of life endpoint	N=40; K=1	SMD 1.23 [0.54, 1.91]
Behavioural individual	Waitlist	Quality of life endpoint	N=28; K=1	SMD 1.03 [0.22, 1.83]
CBT group + any AD	Any AD	Functional impairment at 12-month follow-up	N=62; K=1	SMD -0.92 [-1.45, -0.40]
CBT group + any AD	Any AD	Quality of life physical health component endpoint	N=62; K=1	SMD 0.94 [0.41, 1.47]
CBT group + any AD	Any AD	Quality of life physical health component at 12-month follow-up	N=62; K=1	SMD 1.37 [0.81, 1.93]
CBT group + any AD	Any AD	Quality of life mental health component endpoint	N=62; K=1	SMD 1.40 [0.84, 1.96]
CBT group + any AD	Any AD	Quality of life mental health component at 12-month follow-up	N=62; K=1	SMD 2.11 [1.48, 2.74]
Problem solving group	TAU	Functional impairment endpoint	N=112; K=1	SMD -0.73 [-1.11, -0.34]
Self-help	Waitlist	Quality of life physical health component endpoint	N=204; K=1	SMD 0.63 [0.35, 0.91]
Self-help	Waitlist	Quality of life mental health component endpoint	N=204; K=1	SMD 0.52 [0.24, 0.80]
Self-help	Waitlist	Interpersonal functioning endpoint	N=90; K=1	SMD 0.58 [0.16, 1.00]
Self-help with support	No treatment	Functional impairment endpoint	N=613; K=1	SMD -0.59 [-0.75, -0.43]
Exercise group	TAU	Quality of life mental health component endpoint	N=26; K=1	SMD -0.96 [-1.78, -0.14]
Exercise group + CBT group	CBT group	Global functioning endpoint	N=54; K=1	SMD 1.49 [0.88, 2.10]
Mindfulness/ meditation group	Waitlist	Quality of life endpoint	N=60; K=1	SMD 1.27 [0.71, 1.83]
Mindfulness/ meditation group + any AD	Any AD	Functional impairment endpoint	N=30; K=1	SMD -1.42 [-2.23, -0.60]

Abbreviations: AD=antidepressant; CBT=cognitive behavioural therapy; SMD=standardised mean difference; TAU=treatment as usual

Follow-up of critical outcomes

See Table 14 for a summary of the clinically important and statistically significant effects observed for critical outcomes at longer-term (at least 6 months) follow-up. See supplement B2 for forest plots for all critical outcomes at all follow-up time points.

Table 14. Summary of significant critical outcomes at longer-term (at least 6 months) follow-up for adults with a new episode of less severe depression

Intervention	Control	Outcome	Participants (N); Studies (K)	Effect estimate (95% CI)
CBT group	TAU	Depression symptoms at 12-month follow-up	N=170; K=1	SMD -1.32 [-1.65, -0.99]
CBT group + any AD	Any AD	Depression symptoms at 12-month follow-up	N=62; K=1	SMD -2.98 [-3.71, -2.24]
Problem solving group	TAU	Depression symptoms at 6-month follow-up	N=173; K=1	SMD -1.05 [-1.37, -0.73]
Problem solving group	TAU	Depression symptoms at 12-month follow-up	N=173; K=1	SMD -1.14 [-1.46, -0.82]
Short-term psychodynamic psychotherapy individual	Non-directive counselling individual	Depression symptoms at 6-month follow-up	N=88; K=1	SMD -0.82 [-1.27, -0.37]
Short-term psychodynamic psychotherapy individual	Non directive counselling individual	Remission at 6-month follow-up	N=88; K=1	RR 1.60 [1.14, 2.25]

Abbreviations: AD=antidepressant; CBT=cognitive behavioural therapy; SMD=standardised mean difference; TAU=treatment as usual

Comparison of the results of the results of pairwise meta-analysis with the NMA for critical outcomes

See Table 15 for comparisons between pairwise and NMA results (base-case analysis) for critical outcomes where the difference between the pairwise meta-analysis and NMA results is equal to, or larger than, the minimally important difference (MID, defined as SMD -0.5/0.5 or logOR ±0.25 [MID for OR calculated as exp[0.25]=1.28]) and the effect estimate of the NMA is *not* within the 95% confidence interval of the pairwise effect estimate (considered a significant difference), and see Table 16 for differences between pairwise and NMA results ≥MID but where the NMA effect estimate is within the 95% confidence interval of the pairwise effect estimate (considered a non-significant difference). The full table of pairwise meta-analysis and NMA comparisons is available in supplement B4. Out of a total of 93 comparisons between pairwise and NMA results for less severe depression, 26 differences ≥MID were identified (28% of all comparisons), of these only 11 differences (12% of all comparisons) could be considered significant in that the NMA estimate was not within the 95% confidence interval of the pairwise effect estimate. For most differences identified the difference was in magnitude rather than direction of effect and could probably be accounted for by the smaller evidence base contributing to the pairwise effect estimates. It is important to note that these comparisons have been performed in addition to the NMA inconsistency checks (where direct and indirect evidence is compared). For the NMA inconsistency checks, no evidence of inconsistency was identified in any of the outcomes considered in the clinical analysis.

Table 15. Summary of differences between pairwise and NMA results ≥ MID where NMA effect estimate is not within 95% confidence interval of pairwise effect estimate for adults with a new episode of less severe depression

Intervention	Control	Outcome	Pairwise effect estimate (95% CI)	NMA effect estimate (95% CrI)
Behavioural group	TAU	Depression symptoms SMD	-1.71 [-2.09, -1.33]	-0.93 [-2.16, 0.36]
Behavioural group	Self-help	Depression symptoms SMD	0.17 [-0.05, 0.38]	-0.55 [-1.81, 0.66]
CBT group	No treatment	Depression symptoms SMD	-0.97 [-1.38, -0.56]	-1.48 [-2.24, -0.6]
CBT group	Behavioural group	Depression symptoms SMD	0.20 [-0.10, 0.50]	-0.36 [-1.82, 1.11]
CBT group	Mindfulness/ meditation group	Depression symptoms SMD	0.77 [-0.09, 1.63]	-0.43 [-1.84, 1.03]
Problem solving group	TAU	Depression symptoms SMD	-2.45 [-2.85, -2.05]	-1.46 [-3.22, 0.35]
Self-help	Exercise individual	Depression symptoms SMD	-0.70 [-0.96, -0.43]	0.11 [-1.5, 1.77]
Self-help with support	No treatment	Remission (ITT) OR	1.26 [0.75, 2.11]	2.9 [1.1, 10.4]
Self-help with support	Attention placebo	Depression symptoms SMD	-1.22 [-1.90, -0.54]	-0.3 [-0.72, 0.13]
Mindfulness/ meditation group	No treatment	Depression symptoms SMD	-3.03 [-3.83, -2.24]	-1.02 [-2.39, 0.13]
Yoga group	No treatment	Depression symptoms SMD	-2.38 [-3.50, -1.26]	-1.25 [-2.93, 0.41]

Abbreviations: CBT=cognitive behavioural therapy; CI=confidence interval; ITT=intention-to-treat; NMA=network meta-analysis; OR=odds ratio; SMD=standardised mean difference; TAU=treatment as usual

Table 16. Summary of differences between pairwise and NMA results ≥ MID where NMA effect estimate is within 95% confidence interval of pairwise effect estimate for adults with a new episode of less severe depression

Intervention	Control	Outcome	Pairwise effect estimate (95% CI)	NMA effect estimate (95% CrI)
Behavioural individual	Waitlist	Response (ITT) OR	5.50 [1.15, 26.41]	8.11 [0.52, 124]
Behavioural group	Waitlist	Depression symptoms SMD	-2.93 [-8.00, 2.15]	-1.24 [-2.48, -0.02]
CBT individual	Waitlist	Remission (ITT) OR	5.88 [2.59, 13.31]	4.09 [1.11, 12.75]
CBT group	Waitlist	Depression symptoms SMD	-3.00 [-4.60, -1.39]	-1.61 [-2.35, -0.72]
CBT group	Problem solving group	Depression symptoms SMD	-0.39 [-1.12, 0.35]	0.17 [-1.76, 2.12]
Problem solving individual	Attention placebo	Depression symptoms SMD	-0.65 [-1.50, 0.20]	-0.03 [-1.81, 1.73]
Problem solving group	TAU	Remission (ITT) OR	27.26 [11.86, 62.68]	28.64 [4.64, 181.1]
Self-help	No treatment	Depression symptoms SMD	-1.07 [-1.96, -0.18]	-0.55 [-0.88, -0.24]
Self-help	Attention placebo	Remission (ITT) OR	13.00 [1.51, 111.78]	5.26 [0.47, 104.1]
Mindfulness/ meditation individual	Waitlist	Response (ITT) OR	5.83 [1.30, 26.22]	7.49 [0.34, 172.4]

Exercise individual	No treatment	Depression symptoms SMD	-0.02 [-0.80, 0.76]	-0.67 [-2.33, 0.96]
Exercise individual	Waitlist	Depression symptoms SMD	-1.31 [-1.92, -0.71]	-0.8 [-2.44, 0.82]
Exercise group	Attention placebo	Depression symptoms SMD	-1.27 [-2.04, -0.50]	-0.6 [-3.78, 2.62]
Exercise group	Attention placebo	Response (ITT) OR	3.93 [0.88, 17.56]	5.47 [0.91, 33.03]
Yoga group	Attention placebo	Remission (ITT) OR	13.91 [1.54, 125.63]	21.34 [1.49, 828.9]

Abbreviations: CBT=cognitive behavioural therapy; CI=confidence interval; ITT=intention-to-treat; NMA=network meta-analysis; OR=odds ratio; SMD=standardised mean difference; TAU=treatment as usual

Pairwise meta-analysis of couple interventions

No relevant studies were identified for couple interventions for adults with less severe depression and problems in the relationship with their partner.

Subgroup analysis of studies included in the NMA

Subgroup analysis was only possible for older adults (60 years and older) compared to younger adults (younger than 60 years), and not men or BME populations. Subgroup differences were examined for outcomes that had more than 2 studies in each subgroup. Subgroup analysis was only possible for 1 comparison: exercise individual versus waitlist with 2 RCTs included for older adults (Bernard 2014; McNeil 1991) and 3 RCTs included for younger adults (Doyne 1987; Legrand 2014; Nystrom 2017).

There were no significant subgroup differences between older and younger adults for the comparison exercise individual versus waitlist on: depression symptoms endpoint (Test for subgroup differences: $Chi^2 = 1.40$, df = 1, p = 0.24); depression symptoms change score (Test for subgroup differences: $Chi^2 = 0.14$, df = 1, p = 0.71); discontinuation due to any reason (Test for subgroup differences: $Chi^2 = 0.16$, df = 1, p = 0.69).

Quality assessment of studies included in the evidence review and the evidence

A threshold analysis was originally planned to conduct, to test the robustness of treatment recommendations based on the NMA, to potential biases or sampling variation in the included evidence. Threshold analysis has been developed as an alternative to GRADE for assessing confidence in guideline recommendations based on network meta-analysis (Phillippo 2019). Threshold analysis suggests by how much effects that have been estimated in the NMA need to change before recommendations change, and whether such changes might potentially occur due to bias in the evidence. The NICE Guidelines Technical Support Unit (TSU) attended committee discussions on the rationale for recommendations and noted that, in addition to the results of the NMA, the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The TSU advised that as it was difficult to identify a clear decision rule to link the recommendations directly to the NMA results, it was not feasible or helpful to conduct a threshold analysis. CINeMA was also considered as a method to evaluate the confidence in the results from the NMA (Nikolakopoulou 2020). However, this was not possible to carry out, due to the class models being implemented.

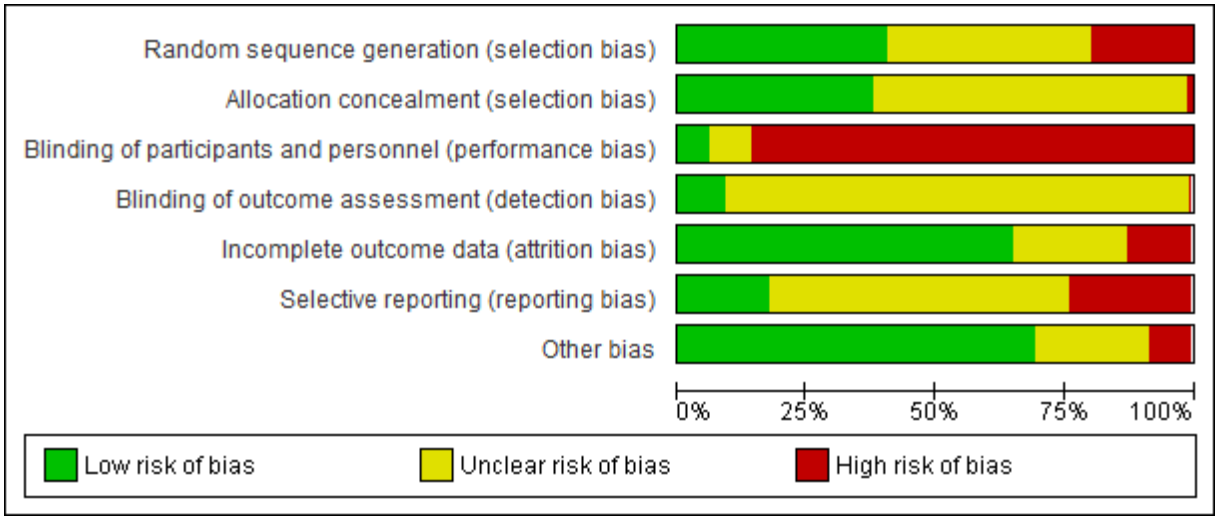
In the absence of undertaking threshold analysis or using CINeMA to evaluate the quality of the evidence and the confidence in the results derived from the NMA that informed this review question, we evaluated and summarise the quality of the evidence narratively, using

the domains considered as per a standard GRADE approach (risk of bias, inconsistency, publication bias, indirectness and imprecision).

Risk of bias

The Cochrane risk of bias tool version 1.0 for RCTs (see appendix H in Developing NICE guidelines: the manual) was used to assess potential bias in each study included in the review. Generally the standard of reporting in studies was quite low, as demonstrated by the risk of bias summary diagram (Figure 8). Of the 142 studies included in the NMAs for less severe depression, 56 were at low risk of bias for allocation method and 53 were at low risk of bias for allocation concealment. Trials of psychological therapies were typically considered at high risk of bias for participant and provider blinding, although it is difficult to quantify in risk of bias ratings it is also important to bear in mind that the rate of side effects may also make it difficult to maintain blinding in pharmacological trials. Across interventions, 8 trials were at low risk of bias for blinding participants and providers. Assessor blinding was considered for all trials including those using self-report measures: 14 were at low risk of bias, 127 were unclear, and high risk in 1 trial. For attrition bias, 90 trials were at low risk of bias, unclear risk in 33 trials, and 19 trials were at high risk of bias. Other sources of bias, potential or actual (for instance, potential conflicts of interest associated with funding), were identified in 45 RCTs. See appendix D for full study details, including risk of bias ratings by study.

Figure 8. Risk of bias summary for treatments of a new episode in people with less severe depression



Model goodness of fit and inconsistency

This section reports only findings of goodness of fit and inconsistency checks for the NMAs that informed the clinical evidence. Respective findings for the NMAs that informed the economic analysis are reported in appendix J. Detailed findings of goodness of fit and inconsistency checks for all NMA analyses, including those that informed the guideline economic model, are reported in appendix M and supplements B5 and B6.

For the SMD of depressive symptom scores, relative to the size of the treatment effect estimates, moderate between trial heterogeneity was observed for this outcome, as expressed by the between-studies standard deviation, following bias adjustment, as described below [τ=0.23 (95% CrI 0.10 to 0.47)]. No evidence of inconsistency was identified with the NMA model having a slightly lower DIC, and similar between study heterogeneity. The inconsistency model did not predict the data substantially better for any data points.

For the outcome of response in those randomised, high between trials heterogeneity was found relative to the size of the intervention effect estimates [τ=0.76 (95% CrI 0.55 to 1.01)]. No evidence of inconsistency was identified with the NMA model having a similar posterior mean residual deviance and lower DIC and between study heterogeneity. The inconsistency model did not predict the data substantially better for any data points, although both consistency and inconsistency models provided a poor fit for Zemestani 2016, which compared waitlist, behavioural activation group and third-wave cognitive therapy group.

For the outcome of remission in those randomised, moderate between trials heterogeneity was found relative to the size of the intervention effect estimates, [τ=0.45 (95% CrI 0.05 to 1.03)]. Posterior mean residual deviances and DIC were similar in the NMA random effects consistency model and the inconsistency model, and there was no clear improvement in the prediction of data in individual studies by the inconsistency model. This suggested that there was no evidence of inconsistency. However, both models poorly predicted data from two studies (Yang 2015, Rosso 2017), both of which investigated No treatment compared to an intervention from the Self-help class. The between-study heterogeneity was very similar in consistency and inconsistency models.

Detailed model fit statistics, heterogeneity and results of inconsistency checks for each outcome are provided in supplements B5 and B6. Comparisons between the relative effects of all pairs of treatments obtained from the consistency (NMA) model and those obtained from the inconsistency (pairwise) model are also provided in supplement B6 for all outcomes considered in the NMA.

Selective outcome reporting and publication bias

Bias adjustment models on the SMD of depressive symptom scores were developed to assess potential bias associated with small study size. Between study heterogeneity and posterior mean residual deviance were lower in the bias-adjusted model that accounted for small study effects, suggesting some evidence of small study bias in comparisons between active and inactive interventions in the SMD outcome, in adults with less severe depression.

The bias adjusted model resulted in moderate changes in the relative effects of all treatment classes versus TAU (reference treatment) and had also a moderate impact on some class rankings. Results are presented in the previous section of this evidence review.

Detailed results of all bias models are provided in appendix M and supplements B5 and B6.

Indirectness

In the context of the NMA, indirectness refers to potential differences across the populations, interventions and outcomes of interest, and those included in the relevant studies that informed the NMA.

A key assumption when conducting NMA is that the populations included in all RCTs considered in the NMA are similar. However, participants in pharmacological and non-pharmacological (psychological or physical intervention) trials may differ to the extent that some participants find different interventions more or less acceptable in light of their personal circumstances and preferences (so that they might be willing to participate in a pharmacological trial but not a psychological one and vice versa). Similarly, self-help trials may recruit participants who would not seek or accept face-to-face interventions. However, a number of trials included in the NMA have successfully recruited participants who are willing to be randomised to either pharmacological or psychological intervention and to either self-help or face-to-face treatment. The NMAs have assumed that service users are willing to accept any of the interventions included in the analyses; in practice, treatment decisions may be influenced by individual values and goals, and people's preferences for different types of interventions. These factors were taken into account when formulating recommendations.

In addition, to explore the transitivity assumption in the context of participants in pharmacological and non-pharmacological trials, a sensitivity analysis on the SMD outcome was conducted after excluding trials with at least one pharmacological or combined intervention arm, where the combined intervention included a pharmacological element. The purpose was to compare the relative effects and rankings of non-psychological treatments between this sensitivity analysis and the base-case analysis. The comparison, which is presented in Table 12, suggested only small changes after exclusion of pharmacological trials, probably because there were not many pharmacological trials included in this dataset (treatments for a new episode of less severe depression).

A post-hoc sensitivity analysis that included only RCTs rated as being at low risk of bias was conducted on the SMD outcome, which was the primary critical outcome of the clinical analysis. Such analysis was only possible to conduct for the domain of 'attrition' in the risk of bias tool, as this was the only domain that included a sufficient number of RCTs at low risk of bias, and a relatively wide range of treatment classes.This sub-group analysis showed no substantial difference in treatment effects compared with the base-case analysis, suggesting that bias from attrition was unlikely to be an effect modifier in this population.

Interventions of similar type were grouped in classes following the committee's advice and considered in class models. These models allowed interventions within each class to have similar, but not identical, effects around a class mean effect. Classes and interventions assessed in the NMAs were directly relevant to the classes and interventions of interest.

Outcomes reported in included studies were also the primary outcomes of interest, as agreed by the committee.

Imprecision

There were wide 95%CrI around mean effects and rankings, for most treatment classes versus the reference treatment (TAU) across all NMA outcomes. For the vast majority of treatment classes, the 95%CrI around relative effects versus TAU crossed the line of no effect.

Overall rating of the quality of the evidence

Based on the narrative assessment of the quality of the evidence using the domains considered as per a standard GRADE approach, the quality of the evidence was considered to be low.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline. See the literature search strategy in appendix B and economic study selection flow chart in appendix G. Details on the hierarchy of inclusion criteria for economic studies are provided in supplement 1 - Methods. For this review question, only economic studies conducted in the UK were included.

The systematic search of the economic literature identified 6 studies that assessed the cost effectiveness of interventions for adults with a new episode of less severe depression in the UK (Kendrick 2005/2006a, Kaltenthaler 2006, Peveler 2005/ Kendrick 2006b, Kendrick 2009, Chalder 2012; Hollingworth 2020). Categorisation of the studies according to their population's severity level of depressive symptoms followed the same criteria used for the categorisation of the clinical studies included in the guideline systematic review. Where study participants' baseline scores on a depressive symptom scale were not provided,

categorisation was based on the description of the participants' depressive symptom severity in the study.

Economic evidence tables are provided in appendix H. Economic evidence profiles are shown in appendix I.

Excluded studies

A list of excluded economic and utility studies, with reasons for exclusion, is provided in supplement 3 - Economic evidence included & excluded studies.

Summary of studies included in the economic evidence review

All included economic studies were conducted in the UK and adopted a NHS perspective, with some studies including personal social service (PSS) costs as well; in addition, some studies reported separate analyses that adopted a societal perspective. NHS and PSS cost elements included, in the vast majority of studies, intervention, primary and community care, staff time (such as GPs, nurses, psychiatrists, psychologists), medication, inpatient and outpatient care and other hospital care. All studies used national unit costs; in some studies, intervention costs were based on local prices or prices provided by the manufacturers (for example in the case of computerised CBT packages).

Problem solving (individual)

Kendrick 2005/2006a evaluated the cost effectiveness of problem-solving treatment provided by mental health nurses compared with generic community mental health nurse care and usual GP care in adults with a new episode of anxiety, depression or reaction to life difficulties, with duration of symptoms between 4 weeks to 6 months, in the UK. The economic analysis was conducted alongside a RCT (Kendrick 2005/2006a, N=247; analysis based on n=184 with clinical data available; cost data available for n=159). The measure of outcome was the QALY, estimated based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 26 weeks.

Under a NHS perspective, problem solving and generic mental health nurse care were found to be significantly more expensive than GP care. The number of QALYs gained was practically the same across all interventions, meaning that GP care was the dominant option. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Self-help (without or with minimal support): computerised cognitive behavioural therapy

Kaltenthaler 2006 undertook decision-analytic economic modelling to assess the cost-utility of computerised CBT versus treatment as usual in adults with depression attending primary care services in the UK. The study evaluated 3 different computerised CBT packages (Beating the Blues; Cope; Overcoming Depression). Efficacy data were taken from analysis of RCT individualised data, other published RCT data and further assumptions. Resource use data were based on manufacturer submissions, published data and other assumptions. The outcome measure was the QALY, based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 18 months.

Based on a NHS perspective, computerised CBT was more costly and more effective than treatment as usual, with an ICER ranging from £2,678 to £10,614 per QALY (depending on package, uplifted to 2020 prices). The probability of computerised CBT being cost-effective ranged from 0.54 to 0.87 at a cost effectiveness threshold of £44,000 per QALY, suggesting that computerised CBT may overall be a cost-effective intervention. The study is directly

applicable to the NICE decision-making context but is characterised by potentially major limitations as a number of input parameters were based on assumptions.

SSRIs

Hollingworth 2020 evaluated the cost effectiveness of sertraline versus placebo in adults presenting to primary care with depression or low mood during the past 2 years. The economic analysis was conducted alongside a RCT (Lewis 2019, N=655; EQ-5D data available for n=505; cost data available for n=381). The measure of outcome was the QALY, estimated based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 12 weeks.

Under a NHS and personal social services perspective, sertraline was found to dominate placebo, as it was both more effective and less costly. Its probability of being cost-effective at the NICE lower cost effectiveness threshold of £20,000/QALY was over 95%. Subgroup analysis showed that sertraline was cost-effective in the treatment of mild, moderate and severe depression. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Kendrick 2009 evaluated the cost effectiveness of provision of SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) in addition to supportive care provided by GPs compared with GP supportive care alone in adults with mild or moderate depression in the UK. The economic analysis was conducted alongside a RCT (Kendrick 2009, N=220; 12-week completers n=196; 6-month followed-up n=160). The measures of outcome were the change in HAMD17 score and the QALY, estimated based on SF-36/SF-6D ratings (UK tariff). The time horizon of the analysis was 12 and 26 weeks.

Under a NHS and social care perspective, SSRI plus supportive care was dominant over supportive care alone at 12 weeks, as it was more effective and had lower total costs. At 26 weeks, SSRI plus supportive care was still more effective but also more costly than supportive care alone, with an ICER of £115 per unit of improvement on HAMD17 or £18,894 per QALY (2020 prices). SSRI plus supportive care had a probability of being cost-effective of more than 0.50 when the cost effectiveness threshold exceeded £94 per unit reduction on HAMD17. At the NICE cost effectiveness threshold of £20,000-£30,000 /QALY, the probability of SSRI plus supportive care reached 0.65-0.75. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

SSRIs versus TCAs

Peveler 2005/Kendrick 2006b evaluated the cost effectiveness of provision of TCAs (amitriptyline, dothiepin or imipramine), SSRIs (fluoxetine, sertraline or paroxetine) and lofepramine (a TCA that was considered in a separate arm) in adults with a new episode of mild-to-moderate depression willing to receive antidepressant treatment in primary care in the UK. The economic analysis was conducted alongside an open-label RCT with a partial preference design: following randomisation, treatment could be prescribed from a different class to the one allocated at random, if participants or their doctor preferred an alternative (N=327; entered preference group n=92; followed-up at 12 months n=171). The measures of outcome were the number of depression-free weeks (DFWs, defined as a HADS-D score <8) and the QALY based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 12 months.

Under a NHS perspective, SSRIs were more costly and more effective than TCAs and lofepramine. Using the number of DFWs as the measure of outcome, TCAs were extendedly dominated (meaning they were less effective and more expensive than a linear combination of the other 2 options). The ICER of SSRI versus lofepramine was £49 per extra DFW. Using the QALY as the measure of outcome, lofepramine was extendedly dominated. The ICER of SSRIs versus TCAs was £4,142/QALY (2020 prices). The probability of SSRIs being cost-

effective was approximately 0.6 at the NICE lower cost effectiveness threshold of £20,000/QALY. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Exercise

Chalder 2012 assessed the cost effectiveness of a physical activity intervention delivered by a physical activity facilitator in addition to usual GP care versus usual GP care alone in adults with a recent first or new depressive episode in the UK. The analysis was conducted alongside a RCT, which was excluded from the clinical analysis due to high attrition rates (N=361; at 12 months EQ-5D data n=195; complete resource use data n=156; multiple imputation used in sensitivity analysis). The outcome measure of the analysis was the QALY, estimated based on EQ-5D (UK tariff). The time horizon of the analysis was 12 months.

Under a NHS and PSS perspective and using only completers' data, the physical activity intervention was found to be more costly and more effective than usual GP care, with an ICER of £24,793/QALY (2020 prices). Its probability of being cost-effective at the NICE lower (£20,000/QALY) and higher (£30,000/QALY) cost effectiveness threshold was 0.49 and 0.57, respectively. Using imputed data, the ICER of the physical activity programme versus usual GP care was £23,079/QALY, while its probability of being cost-effective at the NICE lower and higher cost-effectiveness threshold rose just at 0.50 and 0.60, respectively. The study is directly applicable to the NICE decision-making context but is characterised by potentially serious limitations, mainly its notably high attrition rates.

Economic model

A decision-analytic model was developed to assess the relative cost effectiveness of interventions of adults with a new episode of less severe depression. The objective of economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix J. This section provides a summary of the methods employed and the results of the economic analysis.

Overview of economic modelling methods

A hybrid decision-analytic model consisting of a decision-tree followed by a three-state Markov model was constructed to evaluate the relative cost effectiveness of a range of pharmacological, psychological and physical interventions for the treatment of a new episode of less severe depression in adults treated in primary care. The time horizon of the analysis was 12 weeks of acute treatment (decision-tree) plus 2 years of follow-up (Markov model). The interventions assessed were determined by the availability of efficacy and acceptability data obtained from the NMAs that were conducted to inform this guideline. The selection of classes of interventions was made based on the following criteria:

- The economic analysis assessed only classes of interventions that were included in the NMA of standardised mean difference (SMD), which was the main clinical outcome, as the committee wanted to be able to assess their clinical effectiveness prior to assessing cost-effectiveness. Moreover, to be assessed in the economic analysis, classes needed to be included in the NMAs of discontinuation (for any reason) and response in completers, as these two outcomes informed the economic model.
- Only classes of interventions that had been tested on at least 50 participants (across RCTs) in each of the NMAs of SMD, discontinuation (for any reason) and response in completers were included in the economic analysis, as this was the minimum amount of evidence that a treatment class should have in order to be considered for a practice recommendation. The committee looked at the total size of the evidence base in this area and the large volume of evidence for some treatment classes relative to others, and decided not to consider treatment classes with a small size of evidence base (tested on <50 participants) as there were several treatment classes with a much larger volume of

evidence. An exception to this rule was made for classes of interventions that are routinely available in the NHS, that is, such classes were included in the analysis even if they had been tested on fewer than 50 participants in the NMAs mentioned above. For some treatment classes, inclusion in the economic model was not possible as no data were available on one or more NMA outcomes that informed economic modelling. For such classes, additional relevant data were sought by contacting authors of studies already included in the guideline systematic review, so as to enable inclusion of the classes in the respective NMAs and, subsequently, in the economic modelling.

- In addition, only classes with a higher mean effect on the SMD outcome compared with the selected reference treatment (TAU) were considered in the economic analysis.

Specific interventions were used as exemplars within each class regarding their intervention costs, so that results of interventions can be extrapolated to other interventions of similar resource intensity within their class. The following interventions [in brackets the classes they belong to] were assessed:

- pharmacological interventions: sertraline [SSRIs]; lofepramine [TCAs]
- psychological interventions: cCBT without or with minimal support [self-help without or with minimal support]; cCBT with support [self-help with support]; individual BA [individual BT]; group BA [group BT]; individual CBT (under 15 sessions) [individual CT/CBT]; group CBT (under 15 sessions) [group CT/CBT]; individual problem solving [individual problem solving]; non-directive/supportive/person-centred counselling [individual counselling]; individual IPT [individual IPT]; individual short-term PDPT [individual short-term PDPT]; group MBCT [mindfulness or meditation group]
- physical interventions: supervised high intensity individual exercise [individual exercise]; supervised high intensity group exercise [group exercise]
- GP care, reflected in the RCT arms of the reference treatment [TAU]

The decision-tree component model structure considered the events of discontinuation for any reason and specifically due to intolerable side effects; treatment completion and response/remission; and treatment completion and inadequate or no response. The Markov component model structure considered the states of remission, depressive episode (due to non-remission or relapse), and death. The specification of the Markov component of the model was based on the relapse prevention model developed for this guideline, details of which are provided in the evidence review C, appendix J.

Efficacy data were derived from the guideline systematic review and NMAs. Bias-adjusted analysis suggested no presence of bias due to small study size in the data. Baseline parameters (baseline risk of discontinuation, discontinuation due to side effects, and response/remission) were estimated based on a review of naturalistic studies. The measure of outcome of the economic analysis was the number of QALYs gained. Utility data were derived from a systematic review of the literature, and were generated using EQ-5D measurements and the UK population tariff. The perspective of the analysis was that of health and personal social care services. Resource use was based on published literature, national statistics and, where evidence was lacking, the committee's expert opinion. National UK unit costs were used. The cost year was 2020. Model input parameters were synthesised in a probabilistic analysis. This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. A number of one-way deterministic sensitivity analyses was also carried out.

Results have been expressed in the form of Net Monetary Benefits (NMBs). Incremental mean costs and effects (QALYs) of each intervention versus GP care have been presented in the form of cost effectiveness planes. Results of probabilistic analysis have been summarised in the form of cost-effectiveness acceptability frontiers (CEAFs), which show the treatment option with the highest mean NMB over different cost effectiveness thresholds, and

the probability that the option with the highest NMB is the most cost-effective among those assessed.

Overview of economic modelling results and conclusions

Group CBT appeared to be the most cost-effective intervention, followed by group BA, group exercise, sertraline, group MBCT, cCBT without or with minimal support, lofepramine, and cCBT with support. These were followed by individual CBT, individual BA, individual problem solving, IPT, GP care, non-directive counselling, short-term PDPT, and individual exercise. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

The results of the analysis were characterised by considerable uncertainty, as reflected in the wide 95% credible intervals (CrI) around the rankings of interventions. On the other hand, deterministic sensitivity analysis suggested that the results and the ranking of interventions from the most to the least cost-effective were overall robust under different scenarios explored.

Conclusions from the guideline economic analysis refer mainly to people with depression who are treated in primary care for a new depressive episode; however, they may be relevant to people in secondary care as well, given that clinical evidence was derived from a mixture of primary and secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).

Summary of the evidence

Clinical evidence statements for NMA results

This section reports only NMA results that informed the clinical evidence. Detailed NMA findings on all outcomes, including those that informed the economic analysis, are reported in appendix M and supplements B5 and B6.

Critical outcomes

Depression symptomatology - standardised mean difference (SMD) of depression symptom change scores (bias-adjusted analysis)

- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined CBT group and exercise group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -2.51, 95% CrI -4.42 to -0.61; 25 participants randomised to CBT group + exercise group included in this NMA). Combined CBT group and exercise group is the highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 2.92 [out of 32], 95% CrI 1 to 14).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a problem solving group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -1.52, 95% CrI -3.24 to 0.23; 104 participants randomised to problem solving group included in this NMA). Problem solving group is the second highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 6.61, 95% CrI 1 to 26).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a CBT group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -1.01, 95% CrI -1.76 to -0.06; 480 participants randomised to CBT group included in this NMA). CBT group is the third highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 9.55, 95% CrI 3 to 22).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined mindfulness or meditation group and antidepressant intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -1.23, 95% CrI -5.14 to 2.80; 15 participants randomised to mindfulness/meditation group + antidepressant included in this NMA). Combined mindfulness or meditation group and antidepressant is the fourth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 12.22, 95% CrI 1 to 32).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a behavioural therapy group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.73, 95% CrI -1.95 to 0.50; 340 participants randomised to behavioural therapy group included in this NMA). Behavioural therapy group is the fifth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 13.09, 95% CrI 3 to 28).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual CBT intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.73, 95% CrI -1.78 to 0.36; 481 participants randomised to individual CBT included in this NMA). Individual CBT is the sixth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 13.14, 95% CrI 4 to 27).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a TCA relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.83, 95% CrI -2.18 to 0.53; 136 participants randomised to TCAs included in this NMA). TCAs are the seventh highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 13.27, 95% CrI 3 to 29).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined CBT group and antidepressant intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -1.00, 95% CrI -4.47 to 2.61; 32 participants randomised to CBT group + antidepressant included in this NMA). Combined CBT group and antidepressant is the eighth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 13.34, 95% CrI 1 to 32).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined acupuncture and non-directive counselling intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.78, 95% CrI -2.57 to 1.02; 40 participants randomised to acupuncture + counselling included in this NMA). Combined acupuncture and non-directive counselling is the ninth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 13.37, 95% CrI 2 to 31).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a yoga group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.73, 95% CrI -2.43 to 0.98; 73 participants randomised to yoga group included in this NMA). Yoga group is the tenth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 13.83, 95% CrI 2 to 31).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of acupuncture relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.69, 95% CrI -2.50 to 1.13; 40 participants randomised to acupuncture included in this NMA). Acupuncture is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 14.26, 95% CrI 2 to 31).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a mindfulness or meditation group intervention relative to TAU on depression

symptomatology for adults with less severe depression (SMD -0.62, 95% CrI -1.77 to 0.35; 376 participants randomised to mindfulness/meditation group included in this NMA). Mindfulness/meditation group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 14.47, 95% CrI 4 to 28).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual behavioural therapy intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.63, 95% CrI -2.48 to 1.28; 147 participants randomised to individual behavioural therapy included in this NMA). Individual behavioural therapy is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 14.72, 95% CrI 2 to 31).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an SSRI relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.64, 95% CrI -1.87 to 0.53; 207 participants randomised to SSRIs included in this NMA). SSRIs are outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 15.90, 95% CrI 4 to 30).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual mindfulness or meditation intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.52, 95% CrI -3.10 to 2.22; 20 participants randomised to individual mindfulness/meditation included in this NMA). Individual mindfulness/meditation is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 16.09, 95% CrI 1 to 32).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a short-term psychodynamic psychotherapy intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.48, 95% CrI -2.96 to 2.03; 49 participants randomised to short-term psychodynamic psychotherapy included in this NMA). Short-term psychodynamic psychotherapy is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 16.49, 95% CrI 2 to 32).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual IPT intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.5, 95% CrI -1.94 to 0.83; 153 participants randomised to IPT included in this NMA). IPT is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 16.93, 95% CrI 4 to 30).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a relaxation group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.42, 95% CrI -2.19 to 1.20; 63 participants randomised to relaxation group included in this NMA). Relaxation group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 17.84, 95% CrI 3 to 32).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of an exercise group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.37, 95% CrI -3.56 to 2.79; 199 participants randomised to exercise group included in this NMA). Exercise group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 17.91, 95% CrI 1 to 32).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of self-help with support relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.33, 95% CrI -0.77 to 0.08; 1286 participants randomised to self-help with support included in this NMA). Self-help with support is

outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 18.22, 95% CrI 11 to 25).

- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of an individual relaxation intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.41, 95% CrI -3.07 to 2.23; 13 participants randomised to individual relaxation included in this NMA). Individual relaxation is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 18.39, 95% CrI 1 to 32).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a non-directive counselling intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.20, 95% CrI -2.82 to 2.5; 55 participants randomised to counselling included in this NMA). Non-directive counselling is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 19.20, 95% CrI 2 to 32).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of an individual exercise intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.26, 95% CrI -1.73 to 1.15; 250 participants randomised to individual exercise included in this NMA). Individual exercise is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 19.43, 95% CrI 4 to 31).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a self-help intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.27, 95% CrI -0.66 to 0.09; 4922 participants randomised to self-help included in this NMA). Self-help (with no or minimal support) is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 19.51, 95% CrI 13 to 25).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a combined individual CBT and exercise group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.18, 95% CrI -2.75 to 2.44; 18 participants randomised to individual CBT + exercise group included in this NMA). Combined individual CBT and exercise group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 19.78, 95% CrI 2 to 32).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a psychoeducation group intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD -0.09, 95% CrI -2.07 to 1.96; 22 participants randomised to psychoeducation group included in this NMA). Psychoeducation group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depressive symptom scores (mean rank 20.80, 95% CrI 3 to 32).
- Evidence from the NMA shows no benefit of an individual problem solving intervention relative to TAU on depression symptomatology for adults with less severe depression (SMD 0.17, 95% CrI -1.53 to 1.91; 98 participants randomised to individual problem solving included in this NMA). Individual problem solving is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 24.28, 95% CrI 6 to 32).

Response in those randomised

- Evidence from the NMA shows a clinically important but not statistically significant benefit of a TCA relative to TAU on response (in those randomised) for adults with less severe depression (163 participants randomised to TCAs included in this NMA). TCAs are the

highest ranked intervention for response in those randomised (mean rank 4.54 [out of 25], 95% CrI 1 to 20).

- Evidence from the NMA shows a clinically important and statistically significant benefit of a problem solving group intervention relative to TAU on response (in those randomised) for adults with less severe depression (89 participants randomised to problem solving group included in this NMA). Problem solving group is the second highest ranked intervention for response in those randomised (mean rank 4.86, 95% CrI 1 to 18).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an SSRI relative to TAU on response (in those randomised) for adults with less severe depression (159 participants randomised to SSRIs included in this NMA). SSRIs are the third highest ranked intervention for response in those randomised (mean rank 6.27, 95% CrI 1 to 21).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a CBT group intervention relative to TAU on response (in those randomised) for adults with less severe depression (341 participants randomised to CBT group included in this NMA). CBT group is the fourth highest ranked intervention for response in those randomised (mean rank 8.32, 95% CrI 2 to 18).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a behavioural therapy group intervention relative to TAU on response (in those randomised) for adults with less severe depression (184 participants randomised to behavioural therapy group included in this NMA). Behavioural therapy group is the fifth highest ranked intervention for response in those randomised (mean rank 8.86, 95% CrI 2 to 20).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an exercise group intervention relative to TAU on response (in those randomised) for adults with less severe depression (52 participants randomised to exercise group included in this NMA). Exercise group is the sixth highest ranked intervention for response in those randomised (mean rank 9.27, 95% CrI 2 to 20).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined acupuncture and non-directive counselling intervention relative to TAU on response (in those randomised) for adults with less severe depression (40 participants randomised to acupuncture + counselling included in this NMA). Combined acupuncture and non-directive counselling is the seventh highest ranked intervention for response in those randomised (mean rank 10.30, 95% CrI 1 to 24).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual behavioural therapy intervention relative to TAU on response (in those randomised) for adults with less severe depression (65 participants randomised to individual behavioural therapy included in this NMA). Individual behavioural therapy is the eighth highest ranked intervention for response in those randomised (mean rank 10.40, 95% CrI 1 to 23).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a yoga group intervention relative to TAU on response (in those randomised) for adults with less severe depression (65 participants randomised to yoga group included in this NMA). Yoga group is the ninth highest ranked intervention for response in those randomised (mean rank 10.51, 95% CrI 1 to 24).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of acupuncture relative to TAU on response (in those randomised) for adults with less severe depression (40 participants randomised to acupuncture included in this NMA). Acupuncture is the tenth highest ranked intervention for response in those randomised (mean rank 10.81, 95% CrI 1 to 24).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual mindfulness or meditation intervention relative to TAU on response (in those randomised) for adults with less severe depression (20 participants randomised to

individual mindfulness/meditation included in this NMA). Individual mindfulness/meditation is outside the top-10 highest ranked interventions for response in those randomised (mean rank 11.06, 95% CrI 1 to 24).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual CBT intervention relative to TAU on response (in those randomised) for adults with less severe depression (121 participants randomised to individual CBT included in this NMA). Individual CBT is outside the top-10 highest ranked interventions for response in those randomised (mean rank 12.16, 95% CrI 1 to 24).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a mindfulness or meditation group intervention relative to TAU on response (in those randomised) for adults with less severe depression (197 participants randomised to mindfulness/meditation group included in this NMA). Mindfulness/meditation group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 12.76, 95% CrI 4 to 22).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual exercise intervention relative to TAU on response (in those randomised) for adults with less severe depression (71 participants randomised to individual exercise included in this NMA). Individual exercise is outside the top-10 highest ranked interventions for response in those randomised (mean rank 14.24, 95% CrI 5 to 23).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a self-help intervention relative to TAU on response (in those randomised) for adults with less severe depression (4373 participants randomised to self-help included in this NMA). Self-help (with no or minimal support) is outside the top-10 highest ranked interventions for response in those randomised (mean rank 15.23, 95% CrI 10 to 19).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a psychoeducation group intervention relative to TAU on response (in those randomised) for adults with less severe depression (22 participants randomised to psychoeducation group included in this NMA). Psychoeducation group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 15.36, 95% CrI 2 to 25).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of self-help with support relative to TAU on response (in those randomised) for adults with less severe depression (849 participants randomised to self-help with support included in this NMA). Self-help with support is outside the top-10 highest ranked interventions for response in those randomised (mean rank 15.62, 95% CrI 10 to 21).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a relaxation group intervention relative to TAU on response (in those randomised) for adults with less severe depression (63 participants randomised to relaxation group included in this NMA). Relaxation group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 15.91, 95% CrI 2 to 25).
- Evidence from the NMA shows no benefit of individual IPT relative to TAU on response (in those randomised) for adults with less severe depression (69 participants randomised to IPT included in this NMA). IPT is outside the top-10 highest ranked interventions for response in those randomised (mean rank 18.48, 95% CrI 4 to 25).
- Evidence from the NMA shows a lower effect of an individual relaxation intervention relative to TAU on response (in those randomised) for adults with less severe depression (15 participants randomised to individual relaxation included in this NMA), although this difference is not statistically significant. Individual relaxation is ranked second from bottom for response in those randomised, and is ranked below attention placebo, TAU and enhanced TAU (mean rank 21.53, 95% CrI 4 to 25).

Remission in those randomised

- Evidence from the NMA shows a clinically important and statistically significant benefit of a problem solving group intervention relative to TAU on remission (in those randomised) for adults with less severe depression (89 participants randomised to problem solving group included in this NMA). Problem solving group is the highest ranked intervention for remission in those randomised (mean rank 1.59 [out of 15], 95% CrI 1 to 5).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a yoga group intervention relative to TAU on remission (in those randomised) for adults with less severe depression (20 participants randomised to yoga group included in this NMA). Yoga group is the second highest ranked intervention for remission in those randomised (mean rank 4.58, 95% CrI 1 to 14).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual CBT intervention relative to TAU on remission (in those randomised) for adults with less severe depression (233 participants randomised to individual CBT included in this NMA). Individual CBT is the third highest ranked intervention for remission in those randomised (mean rank 5.38, 95% CrI 2 to 11).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual behavioural therapy intervention relative to TAU on remission (in those randomised) for adults with less severe depression (16 participants randomised to individual behavioural therapy included in this NMA). Individual behavioural therapy is the fourth highest ranked intervention for remission in those randomised (mean rank 5.45, 95% CrI 1 to 13).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of self-help with support relative to TAU on remission (in those randomised) for adults with less severe depression (348 participants randomised to self-help with support included in this NMA). Self-help with support is the fifth highest ranked intervention for remission in those randomised (mean rank 5.72, 95% CrI 2 to 10).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual mindfulness or meditation intervention relative to TAU on remission (in those randomised) for adults with less severe depression (20 participants randomised to individual mindfulness/meditation included in this NMA). Individual mindfulness/meditation is the sixth highest ranked intervention for remission in those randomised (mean rank 6.57, 95% CrI 2 to 14).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a CBT group intervention relative to TAU on remission (in those randomised) for adults with less severe depression (117 participants randomised to CBT group included in this NMA). CBT group is the seventh highest ranked intervention for remission in those randomised (mean rank 7.02, 95% CrI 2 to 13).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a behavioural therapy group intervention relative to TAU on remission (in those randomised) for adults with less severe depression (68 participants randomised to behavioural therapy group included in this NMA). Behavioural therapy group is the eighth highest ranked intervention for remission in those randomised (mean rank 7.49, 95% CrI 2 to 14).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a self-help intervention relative to TAU on remission (in those randomised) for adults with less severe depression (1050 participants randomised to self-help included in this NMA). Self-help (with no or minimal support) is the ninth highest ranked intervention for remission in those randomised (mean rank 7.74, 95% CrI 4 to 11).
- Evidence from the NMA shows no benefit of individual IPT relative to TAU on remission (in those randomised) for adults with less severe depression (69 participants randomised to IPT included in this NMA). IPT is the tenth highest ranked intervention for remission in those randomised (mean rank 9.81, 95% CrI 3 to 15).

- Evidence from the NMA shows a lower effect of a relaxation group intervention relative to TAU on remission (in those randomised) for adults with less severe depression (63 participants randomised to relaxation group included in this NMA), although this difference is not statistically significant. Relaxation group is ranked fourth from the bottom for remission in those randomised (mean rank 10.48, 95% CrI 2 to 15).
- Evidence from the NMA shows a lower effect of an individual relaxation intervention relative to TAU on remission (in those randomised) for adults with less severe depression (15 participants randomised to individual relaxation included in this NMA), although this difference is not statistically significant. Individual relaxation is ranked bottom for remission in those randomised, and is ranked below TAU, waitlist and attention placebo (mean rank 13.64, 95% CrI 5 to 15).

Clinical evidence statements for pairwise meta-analysis results of studies included in the NMA

Important, but not critical, outcomes

Quality of life

- Single-RCT evidence (N=40) shows a clinically important and statistically significant benefit of an individual behavioural therapy intervention relative to no treatment on quality of life for adults with less severe depression.
- Single-RCT evidence (N=28) shows a clinically important and statistically significant benefit of an individual behavioural therapy intervention relative to waitlist on quality of life for adults with less severe depression.
- Single-RCT evidence (N=62) shows clinically important and statistically significant benefits of a combined CBT group and antidepressant intervention relative to an antidepressant-only on quality of life physical health component and mental health component scores at endpoint and 12-month follow-up for adults with less severe depression.
- Single-RCT evidence (N=204) shows clinically important and statistically significant benefits of self-help relative to waitlist on quality of life physical health component and mental health component scores for adults with less severe depression.
- Single-RCT evidence (N=26) shows a clinically important and statistically significant benefit of an exercise group intervention relative to TAU on quality of life mental health component score for adults with less severe depression.
- Single-RCT evidence (N=60) shows a clinically important and statistically significant benefit of a mindfulness or meditation group intervention relative to waitlist on quality of life for adults with less severe depression.

Personal, social and occupational functioning

- Single-RCT evidence (N=62) shows a clinically important and statistically significant benefit of a combined CBT group and antidepressant intervention relative to an antidepressant-only on functional impairment at 12-month follow-up for adults with less severe depression.
- Single-RCT evidence (N=112) shows a clinically important and statistically significant benefit of a problem solving group intervention relative to TAU on functional impairment for adults with less severe depression.
- Single-RCT evidence (N=90) shows a clinically important and statistically significant benefit of self-help relative to waitlist on interpersonal functioning for adults with less severe depression.
- Single-RCT evidence (N=613) shows a clinically important and statistically significant benefit of self-help with support relative to no treatment on functional impairment for adults with less severe depression.

- Single-RCT evidence (N=54) shows a clinically important and statistically significant benefit of a combined exercise group and CBT group intervention relative to CBT group-only on global functioning for adults with less severe depression.
- Single-RCT evidence (N=30) shows a clinically important and statistically significant benefit of a combined mindfulness or meditation group and antidepressant intervention relative to antidepressant-only on functional impairment for adults with less severe depression.

Economic evidence statements

- Evidence from 1 single UK study conducted alongside a RCT (N = 247) suggests that individual problem solving is unlikely to be cost-effective compared with treatment as usual in adults with a new episode of less severe depression. The evidence is directly applicable to the UK context and is characterised by minor limitations.
- Evidence from 1 UK modelling study suggests that computerised CBT (with minimal support) may be potentially cost-effective compared with treatment as usual in adults with a new episode of less severe depression. The evidence is directly applicable to the UK context and is characterised by potentially serious limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N = 655) suggests that sertraline is very likely to be cost-effective compared with placebo in adults with a new episode of less severe depression. The evidence is directly applicable to the UK context and is characterised by minor limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N = 220) indicates that provision of SSRIs in addition to GP supportive care is likely to be cost-effective compared with GP supportive care alone in adults with a new episode of less severe depression. The evidence is directly applicable to the UK context and is characterised by minor limitations.
- Evidence from 1 single UK study conducted alongside an open label RCT with a partial preference design (N = 327; entering preference group n=92) indicates that provision of SSRIs is likely to be more cost-effective than TCAs or lofepramine in adults with a new episode of less severe depression. The evidence is directly applicable to the UK context and is characterised by minor limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N = 361) suggests that a physical exercise programme is potentially cost-effective compared with treatment as usual in adults with a new episode of less severe depression. The evidence is directly applicable to the UK context but is characterised by potentially serious limitations.
- Evidence from the guideline economic modelling suggests that group CBT is likely to be the most cost-effective option for the treatment of new episodes of less severe depression in adults, followed by group BA, group exercise, sertraline, group MBCT, cCBT without or with minimal support, lofepramine, and cCBT with support. These were followed by individual CBT, individual BA, individual problem solving, IPT, GP care, non-directive counselling, short-term PDPT, and individual exercise. This evidence refers mainly to people treated in primary care for a new depressive episode; however, it may be relevant to people treated in secondary care as well, given that clinical evidence was derived from a mixture of primary and secondary care settings. The economic analysis is directly applicable to the NICE decision-making context and is characterised by minor limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify the most effective and cost-effective treatments for less severe depression and the committee chose depression symptomatology (measured as the standardised mean difference, SMD, of depression symptom change scores at treatment endpoint), remission (in those randomised) and response (in those randomised) as critical outcomes to provide an indication of clinical effectiveness. Discontinuation due to side effects and discontinuation for any reason were also chosen as critical outcomes, as indicators of the tolerability and acceptability of treatments, but results for these outcomes were used as part of the economic modelling (along with remission and response in completers) and were not reviewed by the committee separately.

In addition to the critical, depression-specific, outcomes, the committee prioritised 2 important outcomes – these were quality of life and personal, social and occupational functioning. These were selected to determine if treatments for depression led to improved quality of life, and if they helped overcome other difficulties such as ability to sleep, participate in employment, and carry out activities of daily living. These were selected as important and not critical outcomes as the committee were aware that there was likely to be less evidence for these outcomes. The committee recognised that although these outcomes were very important to people with depression, as they would not be available for all interventions they would be less useful to the committee to make recommendations.

The critical outcomes were assessed at treatment endpoint, but in order to determine if treatments for depression had longer term benefits, follow-up measurements of depression symptomatology, remission and response were analysed. Outcomes at these additional timepoints were also assessed by the committee as part of their decision-making process. However, the committee recognised that although these longer-term outcomes were very important to people with depression, as they would not be available for all interventions they would be less useful to the committee to make recommendations.

For each outcome, the committee decided to consider only treatment classes that had been tested on at least 50 participants across the RCTs included in the respective NMA, after looking at the total size of the evidence base on treatments for a new episode of less severe depression and noticing that there were several treatment classes with a much larger volume of evidence.

The quality of the evidence

The trials included for this evidence review were individually assessed using the Cochrane risk of bias tool (version 1.0), and the summarised quality of the evidence is presented in the evidence review. Overall, the majority of domains were rated as at low risk, or unclear risk, of bias with the exception of blinding of participants and personnel where there was a high risk of bias due to a lack of therapist and patient blinding in the psychological treatment trials.

Regarding the outcomes considered in the clinical analysis, the between-trial heterogeneity relative to the size of the intervention effect estimates was moderate for the SMD of depression symptom scores and for remission in those randomised, and high for response in those randomised. No evidence of inconsistency was identified in any of the outcomes considered in the clinical analysis. In the analysis of the SMD of depression symptom scores there was evidence of bias associated with small study size. The bias adjusted model resulted in moderate changes in the relative effects of all treatment classes versus TAU (reference treatment) and also had a moderate impact on some class rankings. The committee took this information into account when interpreting the results.

Regarding the outcomes that informed the economic analysis, relative to the size of the intervention effect estimates, the between trial heterogeneity was found to be moderate for discontinuation due to any reason and high for response in completers. Some evidence of inconsistency was identified for the response in completers outcome. No evidence of bias associated with small study size was identified for either outcome utilised in the economic analysis.

The sensitivity analysis on the SMD outcome conducted to explore the transitivity assumption of participants in pharmacological and non-pharmacological studies found that there were no substantial differences in the results when the pharmacological trials were excluded from analysis and thus the transitivity assumptions are acceptable in this population. The committee noted that most of the evidence for this population comes from non-pharmacological trials.

The post-hoc sub-group analysis on the SMD outcome that included only studies at low risk for the attrition domain of the Cochrane risk-of-bias tool showed no substantial difference in treatment effects compared with the base-case analysis. This suggested that bias from attrition was unlikely to be an effect modifier in this population.

The committee noted that the effectiveness of psychological interventions may depend on clinicians' training, expertise and previous experience with specific treatments, as well as patients' needs, preferences and experiences with previous treatments for depression. The committee acknowledged that these factors may have affected, to some extent, the efficacy of treatments in the RCTs included in the NMAs, and also patient outcomes in clinical practice. These issues were considered when interpreting the available evidence, but also when formulating reocmmendations.

A threshold analysis was originally planned, to assess the robustness of the intervention recommendations to potential limitations in the evidence synthesised in NMAs. Threshold analysis suggests by how much effects that have been estimated in the NMA need to change before recommendations change, and whether such changes might potentially occur due to bias in the evidence. The NICE Guidelines Technical Support Unit (TSU) attended committee discussions on the rationale for recommendations and noted that, in addition to the results of the NMA, the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The TSU advised that as it was difficult to identify a clear decision rule to link the recommendations directly to the NMA results, it was not feasible or helpful to conduct a threshold analysis. The committee agreed with the observation that recommendations were based on a pragmatic approach utilising their clinical experience and the need for inclusivity; and their wish for pragmatic recommendations tailored to individual needs and preferences. Therefore they agreed that threshold analysis would not add value to decision making.

Benefits and harms

In developing the recommendations for the treatment of a new episode of depression the committee were mindful of a number of important factors which underpin the effective delivery of care for people with depression. For example, the need to ensure that progress on treatment is properly monitored and reviewed, and that any potential harms of treatment are minimised. The committee agreed that not addressing these factors could lead to poorer engagement with the service, higher attrition, sub-optimal delivery of treatments and consequent poorer outcomes. The committee therefore carried forward and amended a number of recommendations from the previous guideline and added new recommendations, based on their expertise and experience at providing and receiving treatment for depression. These recommendations included that all interventions should be provided in the context of effective assessment, care planning, liaison and outcome monitoring, and that psychological

and psychosocial interventions should be delivered in accordance with appropriate manuals and competence frameworks, and should be supported by effective supervision and audit.

The committee agreed that decisions on treatment should be made in discussion with the person with depression, and recommended that a shared decision should be made. The committee cross-referred to the guideline recommendations on choice of treatment which provided more detailed recommendations on how this shared decision should be made and what should be included in the discussion. It was recognised by the committee that people who have had prior episodes of depression may also have preferences for their treatment based on prior experience or insight into their own depression patterns.

The committee then discussed the results of the clinical and economic analyses and used this information to draft recommendations relating to the use of specific interventions for the treatment of less severe depression. When reviewing the evidence from the network meta-analysis, the committee were aware that a number of important and well-known, often pragmatic, trials were excluded from the NMA, typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. The committee were particularly mindful of the UK-based psychological treatment studies that had been excluded on this basis, due to the relevance to the NHS context. For less severe depression, the committee's knowledge of the results of these trials (Coote & MacLeod, 2012; Cramer et al. 2011; Lambert et al. 2018; Lovell et al. 2008; McClay et al. 2015; Serfaty et al. 2009; Verduyn et al. 2003; Williams et al. 2013, 2018) was brought to bear when interpreting the results of the NMA. The results of these studies were broadly consistent with the evidence from the systematic review, and the committee took this into consideration when making their recommendations.

The committee reviewed the results of the bias-adjusted NMA for less severe depression for the outcome of SMD, compared to treatment as usual. The committee noted that the point estimate for the majority of intervention classes showed an improvement in depression symptoms, but that most also had very wide 95% credible intervals which crossed zero, and therefore there was uncertainty around the effectiveness. The committee noted that the only treatment class for which there was evidence from more than 50 participants, and credible intervals that did not cross zero was group cognitive and cognitive behavioural therapies (CT/CBT). The committee agreed that it would therefore be reasonable to recommend these as treatments of choice in people with less severe depression. The committee also noted that for some other classes of interventions, such as individual CBT, group problem-solving, and group and individual behavioural therapies, the point estimates indicated effectiveness and the credible intervals were narrower (although they crossed zero). There was very litte to differentiate between the other classes based on the bias-adjusted SMD evidence alone.

The committee reviewed the bias-adjusted NMA rankings for the classes of interventions but noted the very wide credible intervals in the ranks provided, and agreed this did not provide any additional information to help them distinguish between the classes. When the SMD for the treatment classes was reviewed by the committee alongside the SMD results for individual interventions within those classes, the committee noted that some individual interventions demonstrated a difference compared to treatment as usual that had not been seen when reviewing the class level data – this included group behavioural activation, individual CBT, group problem-solving and group mindfulness-based cognitive therapy or group mindfulness and meditation.

The committee reviewed the class level NMA results for the outcomes of response and remission in those randomised. For response the results were similar to those seen for SMD, with most treatments showing a point estimate that indicated that they may be effective, but with wide credible intervals that crossed zero. However, group CT/CBT, group problem-solving and group exercise (as well as pill placebo) did not cross the zero line and so the

committee agreed this reinforced some of the results seen for SMD. The committee also noted that for the outcome of response, antidepressants (TCAs and SSRIs) appeared to be more effective than seen for the outcome of SMD. For the outcome of remission, there was only data for a smaller number of classes, but again this was in line with the results seen for response, with group problem-solving appearing to be the most effective treatment based on this outcome.

The committee discussed the sensitivity analysis conducted to determine if the inclusion of pharmacological trials impacted on the results seen for psychological, psychosocial and physical therapies. It was noted that exclusion of the pharmacological studies had small effects on some SMDs compared to treatment as usual, but did not affect the overall results, with the only effective treatment for which there were data on more than 50 participants across RCTs remaining as group CBT.

The evidence for the outcomes of quality of life and functioning, and for follow-up of depression outcomes were, as described above, presented as pairwise analyses. The committee reviewed the outcomes where a clinically important and statistically significant difference had been identified, but noted that the results were all from single studies, many of which were small (some with fewer than 50 participants, most with fewer than 100 participants).

In terms of quality of life and functioning there was some evidence of benefit for individual behavioural therapy, group problem-solving, self-help, group exercise and group mindfulness and meditation when compared to no treatment, waitlist or treatment as usual. The committee noted that these were interventions that had been identified as being effective at treating depression symptoms, and so the limited evidence of a benefit on quality of life and functioning could reinforce a decision to recommend these treatments. There was also evidence for these outcomes for combination therapy with CBT and antidepressants compared to antidepressants alone or mindfulness/meditation and antidepressants compared to antidepressants alone, which indicated that CBT and mindfulness/mediation provide additional benefits. Again the committee agreed that this limited evidence was not sufficient to use as a basis for recommendations on its own, but it did suggest that there may be quality of life and functional benefits from some of these treatments which also appeared effective based on the critical outcomes.

There were very few comparisons from the data on follow-up of depression outcomes that showed a clinically important and statistically significant difference. Group CBT and group problem-solving showed benefits on depression symptoms at follow-up compared to treatment as usual, and CBT with antidepressants showed benefits compared to antidepressants alone. The committee agreed that this provided a useful indication that the results seen from the NMA for group CBT and group problem-solving may be maintained over a longer period. A 6-month follow-up of short-term psychodynamic psychotherapy (STPP) compared to non-directive counselling found a benefit for STPP for the outcomes of depression symptoms and remission at 6 months, but the committee noted that this small amount of evidence did not change their view, based on the NMA results, that these treatments had similar levels of effectiveness.

The final piece of clinical evidence the committee reviewed was the summary of the differences between the pairwise analysis and the NMA results. It was noted that the number of comparisons where there was a significant difference was small (12%), and in the majority of cases that difference was in the magnitude of the effect. The committee agreed that these differences did not add any additional information that they needed to take into account when making their recommendations, and that there were not any different treatments that they would recommend based on the pairwise evidence.

Finally, the committee noted that the very limited evidence for the subgroup analysis of older versus younger people showed no difference and so there was no evidence on which to base any specific recommendations for people of different ages.

Based on their overall review of the clinical evidence the committee agreed that some treatment classes and interventions (group CT/CBT class, group BA, individual CBT forms, group problem solving intervention, MBCT and group mindfulness or meditation, and group exercise) appeared to be more effective than others in ranking, but there was otherwise little to choose between treatments. The committee therefore reviewed the results of the health economic modelling (see separate details of this discussion below) which determined which treatments were cost-effective, and used this to develop a suggested prioritisation of which treatments should be offered to people with depression, or considered for use.

The committee agreed that the likely benefits of recommending specific treatments for less severe depression would be improvements in depression symptoms, and in some cases remission and response. However, given the uncertainty associated with the evidence the committee agreed that the relative benefits and harms are likely to vary across individuals, and it was important that a wide range of interventions were available to take into account individual needs and allow patient choice. The potential harms that the committee identified were side effects and withdrawal effects associated with antidepressant treatment. On the basis of safety and tolerability, the committee advised that SSRIs would be the preferred antidepressants to use in people with less severe depression. Given the potential for side effects and/or withdrawal effects and the availability of psychological and physical treatments that were found to be effective (several of which ranked more highly than antidepressants regarding efficacy), the committee made a strong recommendation that medication should not be the default treatment for people with less severe depression, unless it was the person's preference to take antidepressants rather than engage in a psychological or physical intervention.

As there was limited evidence for the effectiveness of peer support the committee made a research recommendation. As there was uncertainty about the differential effectiveness of psychological treatments, they also made research recommendations about the mode of action of psychological treatments, as this may provide information to support decision-making in the choice of treatments.

A research recommendation about the withdrawal effects of antidepressants was made as there was limited evidence to provide information to patients and support methods of withdrawal. This related to the section of the guideline on starting and stopping antidepressants, which was based on evidence from the NICE guideline on Safe prescribing and so the details of the research recommendation were included in this evidence review.

Cost effectiveness and resource use

According to existing UK economic evidence, computerised CBT (with minimal support) and physical exercise might be potentially cost-effective compared with treatment as usual in adults with a new episode of less severe depression. On the other hand, individual problem solving was unlikely to be cost-effective compared with treatment as usual in this population. Sertraline was likely to be cost-effective compared with placebo, and provision of SSRIs in addition to GP supportive care was likely to be cost-effective compared with GP supportive care alone. SSRIs were also likely to be more cost-effective than TCAs or lofepramine. This evidence was directly applicable to the NICE decision-making context, but methodological limitations ranged from minor to potentially severe.

Existing economic evaluations assessed a limited range of pharmacological, psychological and physical interventions in, mostly, pairwise comparisons, so it was difficult for the committee to draw any robust conclusions on the relative cost effectiveness of the full range of interventions that are available for the treatment of adults with a new episode of less severe depression.

The guideline economic analysis assessed the cost effectiveness of a wide range of pharmacological, psychological and physical interventions, as initial treatments for people with a new episode of less severe depression. The interventions included in the economic

analysis were dictated by availability of data and were used as exemplars within their class regarding intervention costs, as for practical reasons it was impossible to model all interventions considered in the guideline NMA. The committee noted that the results of interventions could be extrapolated, with some caution, to other interventions of similar resource intensity within the same class.

Within each of the individual and group CT/CBT classes, there were two separate interventions of CBT≥15 sessions and CBT<15 sessions. Regarding individual CBT, the two interventions were shown to have a similar SMD vs TAU (individual CBT≥15 sessions -0.68, 95% CrI -1.36 to 0.01; individual CBT<15 sessions -0.66, 95% CrI -1.45 to 0.16), and individual CBT<15 sessions had a somewhat larger evidence base across RCTs on the SMD outcome (N=233 vs 123). Individual CBT<15 sessions was considered to have an appropriate intensity for a population with less severe depression by the committee, it had also a wider evidence base than CBT≥15 sessions, and given that individual CBT≥15 sessions and individual CBT<15 sessions had similar effectiveness, individual CBT<15 sessions was selected for consideration as an exemplar of its class in the economic modelling (which ultimately informed guideline recommendations). Regarding group CBT, group CBT<15 sessions had a better SMD vs TAU than group CBT≥15 sessions (group CBT<15 sessions -1.25, 95% CrI -1.72 to -0.83; group CBT≥15 sessions -0.84, 95% CrI -1.91 to 0.78) and also a much wider evidence base (N=316 vs 10). Therefore, as group CBT<15 sessions was shown to have better effects and a much wider evidence base than group CBT≥15 sessions, it was selected for consideration as an exemplar of its class in the economic modelling (which ultimately informed recommendations). The committee considered group CBT<15 sessions to have appropriate intensity for a population with less severe depression.

The economic analysis included only classes that had been tested on at least 50 participants across RCTs included in the NMAs of the SMD, discontinuation for any reason and response in completers, or fewer than 50 participants if the intervention class was one that was already in routine use in the NHS. These criteria meant that some classes of interventions such as group problem-solving were not included in the economic model. To be considered in the economic analysis, treatment classes should have shown a better mean effect than the reference intervention, which was treatment as usual. This was assumed in the model to reflect GP care. The NMAs of discontinuation (for any reason) and response in completers, which informed the economic analysis, were tested for the presence of bias due to small study size. No evidence of bias was identified.

The economic analysis utilised data on the risk of side effects from antidepressants obtained from a large US study that reported claims data. This risk ranged from 4.7% to 9.2%, depending on the antidepressant class. The committee selected these data because they expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, are more representative of the risk of side effects that have an impact on HRQoL and healthcare costs (which are of interest as they may have an impact on antidepressants' relative cost-effectiveness) compared with studies asking specifically participants to self-report the presence of side effects choosing from a side-effect checklist. According to the committee's expert opinion, the latter study design tends to overestimate the prevalence of side effects. There was also a danger of the risk of side effects from antidepressants being overestimated in the economic model, since the risk of common side effects for psychological therapies was conservatively assumed to be zero. Nevertheless, the committee advised that a higher risk of side effects (40%) be tested in a sensitivity analysis. This had some impact on the relative cost-effectiveness of antidepressants, which was considered when making recommendations.

The committee considered the ranking of interventions for adults with a new episode of less severe depression, from the most to the least cost-effective. According to this ranking, group CBT and group behavioural activation appeared to be the most cost-effective therapies. The majority of the other interventions also appeared to be cost-effective compared with GP care,

with the exception of non-directive counselling, short-term psychodynamic psychotherapy (PDPT) and individual exercise therapy.

The committee considered the 95% credible intervals (CrI) around the rankings of interventions and noted that these were characterised by considerable uncertainty. For example, the mean ranking of group CBT, which was shown to be the most cost-effective intervention, was 2.61, however its 95% CrI were 1 to 12, suggesting uncertainty around the result for group CBT. On the other hand, group CBT dominated most of the other interventions included in the economic analysis (i.e. it was more effective and less costly), or, regarding the few comparisons where it was more effective and more costly (group exercise, self-help and self-help with support and GP care), the respective ICER never exceeded £3,000/QALY, which is well below the NICE lower cost-effectiveness threshold of £20,000/QALY. Similar uncertainty was shown for the rankings of all interventions included in the analysis. On the other hand, deterministic sensitivity analysis suggested that the results and the ranking of interventions were overall robust under different scenarios explored.

The committee noted that there was evidence of clinical and cost-effectiveness for self-help with support (which, in the economic model, was represented by computerised CBT) and discussed that, in practice, and particularly in the IAPT services, it may be more logical to offer self-help with support (usually known in IAPT as 'guided self-help') first. Guided self-help in IAPT services may include materials based on structured CBT, problem solving, psychoeducation and behavioural activation delivered face-to-face or by telephone or online. This is a less intrusive intervention for people with less severe depression, is less resource intensive for IAPT services to deliver, and is likely to be available for people in a timely fashion without the need for a long time on a waiting list. The committee therefore made guided self-help the first suggested option for treatment, before considering a more intensive treatment.

Based on the clinical and cost-effectiveness data, the committee agreed that group CBT or group behavioural activation (BA) were alternative treatments of choice for a new episode of less severe depression in adults, as they had showed a beneficial effect compared to treatment as usual, and appeared to be the most cost-effective classes in the economic analysis. The committee noted that both these treatments were group therapies, and that some people with depression may not wish to attend group treatment. The committee noted that there was evidence of clinical and cost-effectiveness for individual CBT and individual BA and considered offering these as alternatives to people who did not wish to attend group therapy.

The committee did not recommend self-help without support, although this was shown to be more cost-effective than self-help with support, because they acknowledged the importance of building a therapeutic relationship as part of the therapy. They also advised that wider evidence suggests that pure (non-supported) self-help is characterised by lower uptake and adherence compared with self-help with support, which suggests user preference for supported forms of self-help.

The committee agreed that, to allow choice of treatments, a wider range of treatments should be offered – these would provide alternatives to people who did not wish to have guided self-help, CBT or BA, or had tried them for a previous episode of depression and not found them to be effective. The committee discussed that other cost-effective interventions should be included in these alternatives and so recommended group exercise, group mindfulness and meditation, and interpersonal therapy as alternative psychological or physical therapies.

The committee also discussed the role of pharmacological therapy in the treatment of less severe depression. The clinical results for the effect of antidepressants on depression symptoms were similar to those seen for the psychological therapies, showing an improvement in depression symptoms but considerable uncertainty, and the cost-effectiveness results showed both SSRIs and TCAs were likely to be cost-effective (they were placed 4th and 7th in the base-case cost-effectiveness ranking respectively, although

they dropped to 10th and 14th place, respectively, in sensitivity analysis that considered a higher risk of side effects). Given the uncertainty and limitations around the clinical and cost-effectiveness data, the committee considered it important to provide a wide range of interventions including psychological, physical and pharmacological options, to take into account individual needs and allow patient choice. The committee considered the fact that there may be people who do not wish or are not able to participate in a psychological or physical therapy, or may prefer a pharmacological treatment. It was also recognised by the committee that people who have had prior episodes of depression may have preferences for their treatment based on prior experience or insight into their own depression patterns. On this basis, antidepressants (specifically SSRIs as these are generally better tolerated and safer than TCAs) were included as a treatment option for people with less severe depression. However, based on the evidence that some psychological interventions may be more effective, and considering safety and tolerability, the committee agreed that SSRIs should only be considered for use after taking into account other recommended treatment options. Although the committee did not want to prohibit the use of antidepressants where these were the patient's preference, given the potential for side effects and/or withdrawal effects and the availability of effective psychological and physical treatments, the committee made a strong recommendation that medication not be the default treatment for people with less severe depression, unless it was the person's preference to take antidepressants rather than engage in a psychological or physical intervention.

The committee discussed the 3 treatments that were less cost-effective than other treatment options and did not appear to be cost-effective compared with GP care. They agreed not to recommend individual exercise programs as group exercise had been recommended as a cost-effective option, but agreed that there may be some sub-groups of people in whom supportive empathetic counselling may help, particularly those with psychosocial, relationship or employment problems contributing to their depression, and that in these groups counselling may be more cost-effective than in the wider population of people with depression. Similarly, they agreed that short-term PDPT may be useful (and therefore may be more cost-effective) where developmental difficulties in relationships contributed to depression.

The committee discussed the fact that there had been some evidence of effectiveness for group problem-solving but noted that, due to limited data available and the rules for inclusion in the economic model, this had not been included in the health economic model and so they were not able to determine if this was a cost-effective option. Due to this lack of cost-effectiveness data the committee agreed not to recommend group problem-solving as an intervention. Also, they decided not to recommend individual problem solving as a separate intervention although it was more cost-effective than GP care, because it may form part of guided self-help or individual CBT.

The committee were concerned that psychological interventions are not always implemented consistently – for example audits have suggested that reduced numbers of sessions are used in practice compared with what is recommended, and that commissioners may not be clear how many sessions of a particular therapy are required. It was also important for people with depression to be aware of what was involved in the different types of therapy before making a decision. The committee therefore agreed it was important to specify the focus and structure of the psychological interventions being recommended to ensure consistency, and to highlight any particular advantages or drawbacks so that people could make an informed choice. The recommended structure of all psychological interventions (usual number of sessions, as well as optimal number of therapists and participants for group interventions) was based on the resource use utilised in the economic analysis, which, in turn, was informed by RCT resource use, modified by the committee's expert advice to represent optimal routine clinical practice in the UK. In this way, the recommended structure of psychological interventions represents cost-effective use of available healthcare resources as implemented in routine clinical practice. The committee were aware that the suggested number of sessions for some high intensity psychological interventions (such as individual

BA and individual CBT), which was based on available RCT evindence, was at the lower end of the number of sessions usually delivered in IAPT services, but expressed the opinion that these are high intensity interventions and the suggested number of sessions should be usually adequate to improve outcome in people with less severe depression. Nevertheless, the committee agreed that the recommended structure of all psychological interventions should allow flexibility so that more sessions may be provided according to individual needs. The committee made no recommendation on the duration of sessions of psychological interventions, to allow flexibility in their delivery.

The committee agreed that high intensity group interventions should be optimally delivered by 2 therapists, at least one of whom has therapy-specific training and competence, and actively facilitates and leads the delivery of the intervention, while the other therapist makes observations. However, it was noted that there is evidence that MBCT can be successfully delivered by 1 therapist in RCTs. They also agreed that optimal delivery of group interventions should involve small numbers of participants (usually 8), as reflected in respective RCTs; however, they noted that in some MBCT trials the intervention was delivered to larger numbers of participants (up to 15) per group so the respective recommendation suggested a wider range in the number of participants per group. Nevertheless, the suggested 'usual' numbers of participants should only serve as a guide and allow flexibility around the number of participants per group

Other factors the committee took into account

In addition to the results of the network meta-analysis (NMA) the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, implementation factors, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The recommended first-line treatments for less severe depression were included in a table in the guideline in order to support shared decision-making. The treatment options are arranged in the suggested order in which they should be considered. However, the guideline recommends that all treatments in the table can be used as first-line treatments, and that the least intrusive and least resource intensive treatment should be considered first (guided self-help) unless it is not appropriate based on the person's clinical needs and preferences.

The committee discussed that the division of the population for this guideline into 'less severe' and 'more severe' using published cross-walk tables with an anchor score of 16 on the PHQ-9 scale, meant that the less severe population was people with subthreshold symptoms or mild depression only. However, in reality, people with depression are on a continuum, and their feelings and symptoms may vary from day to day, depending on many other factors including what else is happening in their life. Therefore, although the clinical results provided guidance on treatments for depression, the committee agreed that a holistic approach was required with consideration of social causes and available social interventions as well. The committee noted that this was already covered in the guideline in the recommendations on initial assessment of depression, and therefore they did not make any additional recommendations on this in the treatment section of the guideline.

The committee noted that their recommendations for exercise interventions would need to be modified if necessary to ensure that people with disabilities were still able to access this as a treatment option, and they highlighted this in their recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.2 and 1.5.3 and research recommendations in the NICE guideline.

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More severe depression

Review question

For adults with a new episode of more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Clinical evidence

Included studies

A total of 534 randomised controlled trials (RCTs) were included in this evidence review.

In accordance with the review protocol, data from non-English language or unpublished studies was included where it could be extracted from the previous 2009 NICE Depression guideline or from a systematic review, and data was extracted from the following systematic reviews: Cipriani 2018; Geddes 1999; Krogh 2017; Smith 2018.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

The NMAs included 534 RCTs (k=534) representing 89,286 participants (n=89,286).

Of the 534 RCTs included in the NMAs for more severe depression, 426 reported either a HAM-D or MADRS score at baseline, and the mean depression severity scores were HAM-D=24.03 (SD=4.68; k=340) and MADRS=30.01 (SD=5.49; k=86) respectively. 34 were UK-based RCTs.

According to the interventions assessed and the types of outcomes reported in each RCT, the included RCTs have contributed data to one or more networks of evidence and respective NMAs.

For the SMD of depression symptom change scores outcome, the network of evidence (and the respective NMA) included 352 RCTs, 99 interventions grouped in 50 treatment classes, and 59,350 participants. Of the 352 RCTs, 146 reported change from baseline (CFB) depression symptom score data; 172 reported baseline and endpoint depression symptom score data; and 34 reported dichotomous response data and baseline symptom scores. These data were transformed and synthesised accordingly, allowing estimation of the SMD of depression symptom scores (see appendix M for details).

For the outcome of response in those randomised, the network of evidence (and the respective NMA) included 364 RCTs, 83 interventions grouped in 43 treatment classes and 68,073 participants. Of the 364 RCTs, 280 reported dichotomous response data, 31 reported CFB depression symptom score data; and 53 reported baseline and endpoint depression symptom score data. These data were transformed and synthesised accordingly, allowing estimation of log-odds ratios of response (see appendix M for details).

For the outcome of remission in those randomised, the network of evidence (and the respective NMA) included 202 RCTs reporting dichotomous remission data, 64 interventions grouped in 38 treatment classes and 40,066 participants.

See the full evidence tables in appendix D.

Relevant information on the networks of evidence and the NMAs that informed the economic analysis are reported in appendix M.

Evidence from the network meta-analysis

Base-case analysis

Below is an overview of the treatment class network plots, numbers of people tested on each treatment class and intervention, and NMA findings at the treatment class level (relative effects versus the reference treatment and rankings), for every critical outcome considered in the clinical base-case analysis of treatments for adults with a new episode of more severe depression. For the outcome of the SMD of depressive symptom scores, relative effects of individual interventions versus the reference treatment are also provided in this section.

For each outcome, we present network plots, which show which treatments have been directly compared in the RCTs included in the NMA, by connecting them with a direct line. In each network plot presented below, the width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.

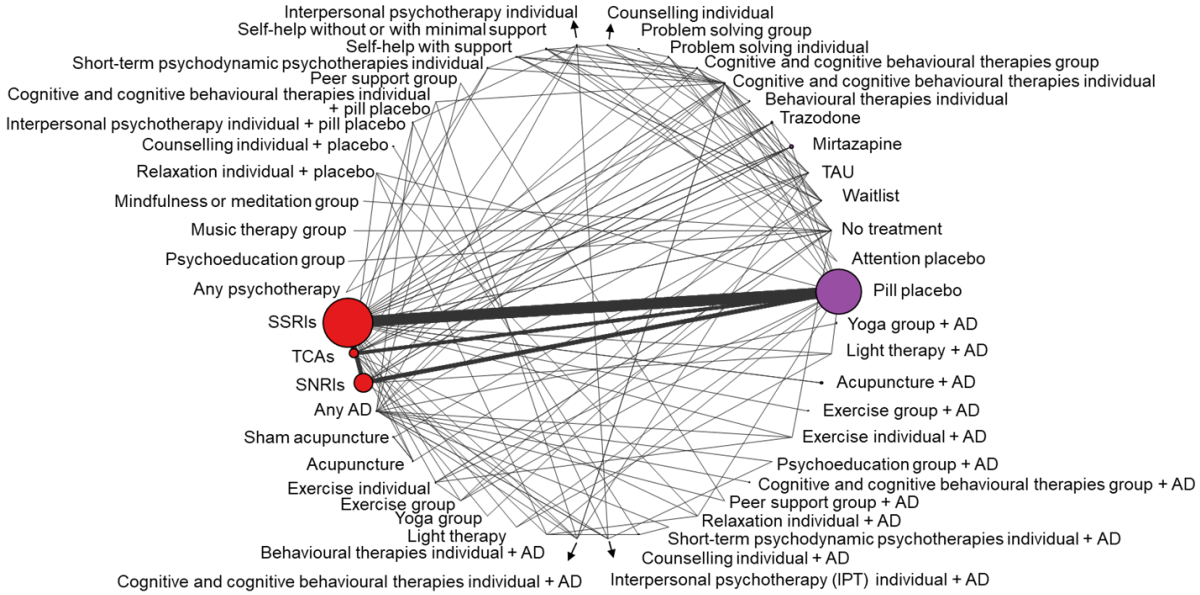
Full results of the NMA, including network plots and relative effects of individual interventions, as well as relative effects of all pairs of treatment classes and individual interventions, are reported in appendix M and supplements B5 and B6.

SMD of depression symptom change scores

The network plot at the treatment class level is shown in Figure 9. The number of participants tested on each treatment class and each intervention are shown in Table 17. Treatment classes, interventions and numbers of participants tested on each in the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression. The base-case relative effects (posterior mean SMD with 95% CrI) of all treatment classes versus pill placebo (reference treatment for more severe depression) are illustrated in

Figure 10 (forest plots) and reported in Table 18. The same table also shows the class treatment rankings. Treatment classes in the table have been ordered from lowest to highest ranking (with lower rankings suggesting greater effects).

Figure 9. Network plot of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression – treatment class level



The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 17. Treatment classes, interventions and numbers of participants tested on each in the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression

Treatment class	N	Intervention	N
Pill placebo	12,554	Pill placebo	12,554
Attention placebo	61	Attention placebo	61
No treatment	504	No treatment	504
Waitlist	526	Waitlist	526
TAU	220	TAU	220
Sham acupuncture	108	Inactive laser acupuncture	34
		Sham electrostimulation at non-specific points with no current	22
		Traditional non-specific point acupuncture	52
Self-help without or with minimal support	344	Cognitive bibliotherapy	159
		Computerised-CBT (CCBT)	120
		Computerised attentional bias modification	26
		Mindfulness meditation CD	39
Self-help with support	267	Cognitive bibliotherapy with support	66
		Computerised-CBT (CCBT) with support	164
		Mindfulness meditation CD with support	19
		Relaxation training CD with support	18
Behavioural therapies individual	378	Behavioural activation (BA) individual	368
		Behavioural therapy (Lewinsohn 1976) individual	10

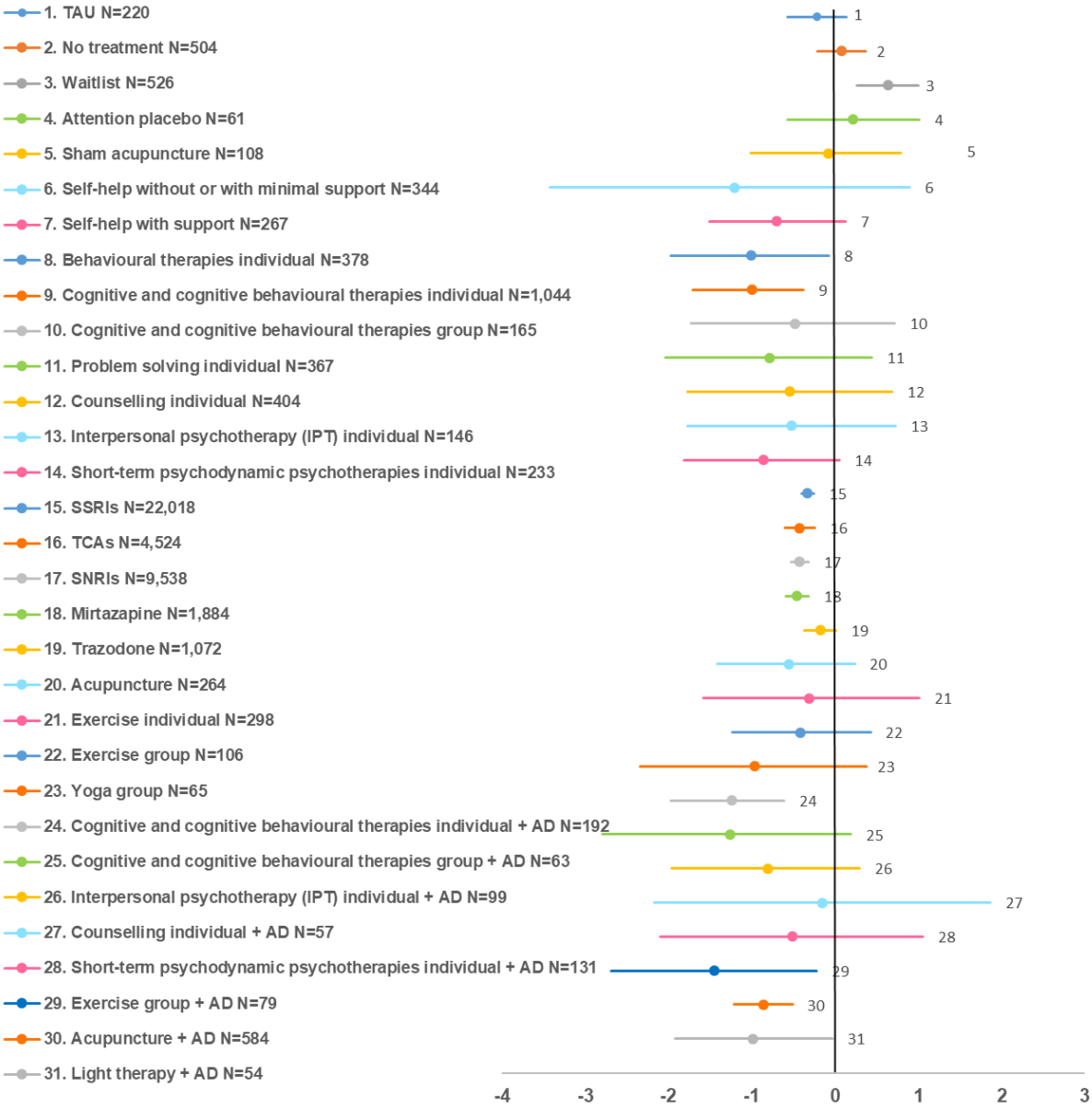
CT/CBT individual	1,044	CBT individual (15 sessions or over)	626
		CBT individual (under 15 sessions)	369
		Dialectical behavioural therapy (DBT) individual	10
		Third-wave cognitive therapy individual	39
CT/CBT group	165	CBT group (under 15 sessions)	165
Problem solving individual	367	Problem solving individual	367
Problem solving group	47	Problem solving group	47
Counselling individual	404	Non-directive/supportive/person-centred counselling	404
IPT individual	146	IPT individual	146
Short-term PDPT individual	233	Dynamic interpersonal therapy (DIT) individual	73
		Short-term PDPT individual	160
Psychoeducation group	44	Psychoeducational group programme	44
Music therapy group	12	Music therapy group	12
Mindfulness or meditation group	15	MBCT group	15
Peer support group	39	Peer support group	39
Any psychotherapy	37	Any psychotherapy	37
CT/CBT individual + pill placebo	61	CBT individual (15 sessions or over) + pill placebo	17
		CBT individual (under 15 sessions) + pill placebo	44
IPT + pill placebo	69	IPT individual + pill placebo	69
Counselling individual + pill placebo	26	Non-directive/supportive/person-centred counselling + pill placebo	26
Relaxation individual + pill placebo	11	Progressive muscle relaxation individual + pill placebo	11
SSRIs	22,018	Any SSRI	207
		Citalopram	2,195
		Escitalopram	4,930
		Fluoxetine	6,031
		Paroxetine	5,861
		Sertraline	2,794
TCAs	4,524	Amitriptyline	2,462
		Any TCA	21
		Clomipramine	345
		Imipramine	1,306
		Lofepramine	145
		Nortriptyline	245
SNRIs	9,538	Duloxetine	5,269
		Venlafaxine	4,269
Mirtazapine	1,884	Mirtazapine	1,884
Trazodone	1,072	Trazodone	1,072
Any AD	452	Any AD	452
Acupuncture	264	Electroacupuncture	110
		Laser acupuncture	39
		Traditional acupuncture	115
Exercise individual	298	Supervised high intensity exercise individual	128
		Supervised low intensity exercise individual	117
		Unsupervised high intensity exercise individual	53

Exercise group	106	Supervised high intensity exercise group	69
		Supervised low intensity exercise group	37
Yoga group	65	Yoga group	65
Light therapy	32	Bright light therapy	32
Behavioural therapies individual + AD	22	Behavioural activation (BA) individual + amitriptyline	12
		Behavioural activation (BA) individual + any AD	10
CT/CBT individual + AD	192	CBT individual (15 sessions or over) + any AD	10
		CBT individual (15 sessions or over) + any SSRI	43
		CBT individual (15 sessions or over) + imipramine	25
		CBT individual (15 sessions or over) + nortriptyline	18
		CBT individual (under 15 sessions) + escitalopram	48
		CBT individual (under 15 sessions) + sertraline	38
		Third-wave cognitive therapy individual + any AD	10
CT/CBT group + AD	63	CBT group (under 15 sessions) + any AD	63
IPT individual + AD	99	IPT individual + any AD	87
		Interpersonal counselling individual + venlafaxine	12
Counselling individual + AD	57	Non-directive/supportive/person-centred counselling + any AD	15
		Non-directive/supportive/person-centred counselling + any SSRI	17
		Non-directive/supportive/person-centred counselling + fluoxetine	25
Short-term PDPT individual + AD	131	Short-term PDPT individual + any AD	113
		Short-term PDPT individual + any SSRI	18
Psychoeducation group + AD	27	Psychoeducational group programme + any AD	27
Peer support group + AD	42	Peer support group + any AD	42
Relaxation individual + AD	10	Progressive muscle relaxation individual + amitriptyline	10
Exercise individual + AD	40	Supervised high intensity exercise individual + any AD	14
		Supervised high intensity exercise individual + sertraline	15
		Supervised low intensity exercise individual + any AD	11
Exercise group + AD	79	Supervised high intensity exercise group + sertraline	42
		Supervised low intensity exercise group + sertraline	37
Yoga group + AD	15	Yoga group + any AD	15
Acupuncture + AD	584	Electroacupuncture + any SSRI	160
		Electroacupuncture + fluoxetine	46
		Electroacupuncture + paroxetine	71
		Traditional acupuncture + any SSRI	206
		Traditional acupuncture + paroxetine	101
Light therapy + AD	54	Bright light therapy + fluoxetine	29

		Bright light therapy + venlafaxine	25

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Figure 10. Base-case forest plots of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression: effects of treatment classes versus pill placebo (N=12,554) Values on the left side of the vertical axis indicate better effect compared with pill placebo. Effects are shown only for treatment classes with N ≥ 50.



AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 18. Base-case results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression: posterior effects (mean SMD, 95%CrI) of all treatment classes versus pill placebo and treatment class rankings

Treatment class	N	SMD vs pill placebo (mean, 95% CrI)	Rank (mean, 95% CrI)
Mindfulness or meditation group	15	**-3.69 (-5.16 to -2.23)**	1.33 (1 to 4)
Problem solving group	47	**-2.37 (-3.76 to -1.00)**	4.05 (1 to 15)
Yoga group + AD	15	**-1.91 (-3.64 to -0.24)**	7.58 (1 to 33)
Exercise group + AD	79	**-1.46 (-2.69 to -0.22)**	10.64 (2 to 33)
Peer support group + AD	42	-1.49 (-3.10 to 0.04)	11.14 (2 to 38)
CT/CBT individual + AD	192	**-1.25 (-1.97 to -0.62)**	11.86 (4 to 23)
Peer support group	39	-1.37 (-2.75 to 0.03)	12.05 (2 to 37)
CT/CBT group + AD	63	-1.27 (-2.80 to 0.19)	13.65 (2 to 39)
Exercise individual + AD	40	**-1.13 (-2.21 to -0.09)**	14.73 (3 to 36)
Self-help without/with minimal support	344	-1.21 (-3.43 to 0.89)	15.21 (2 to 43)
CT/CBT individual	1,044	**-1.00 (-1.71 to -0.38)**	15.89 (6 to 29)
Behavioural therapies individual	378	**-1.01 (-1.98 to -0.08)**	16.21 (4 to 36)
Psychoeducation group	44	-1.05 (-2.41 to 0.31)	16.52 (3 to 40)
Light therapy + AD	54	**-0.99 (-1.92 to -0.04)**	16.59 (4 to 37)
Yoga group	65	-0.97 (-2.34 to 0.38)	17.77 (3 to 41)
Acupuncture + AD	584	**-0.87 (-1.22 to -0.51)**	17.88 (10 to 27)
Relaxation individual + AD	10	-0.96 (-2.68 to 0.78)	18.69 (2 to 42)
Short-term PDPT individual	233	-0.86 (-1.82 to 0.05)	18.99 (5 to 38)
IPT individual + AD	99	-0.81 (-1.96 to 0.29)	20.18 (5 to 40)
Behavioural therapies individual + AD	22	-0.85 (-2.51 to 0.83)	20.21 (3 to 42)
Problem solving individual	367	-0.79 (-2.04 to 0.44)	20.68 (4 to 41)
Light therapy	32	-0.77 (-2.06 to 0.52)	21.14 (4 to 41)
Self-help with support	267	-0.70 (-1.51 to 0.13)	21.74 (8 to 39)
Music therapy group	12	-0.56 (-2.10 to 0.97)	24.87 (4 to 43)
Acupuncture	264	-0.56 (-1.42 to 0.23)	25.13 (9 to 40)
Counselling individual	404	-0.55 (-1.78 to 0.68)	25.17 (6 to 42)
Short-term PDPT + AD	131	-0.51 (-2.10 to 1.06)	25.60 (4 to 43)
IPT individual	146	-0.52 (-1.77 to 0.72)	25.66 (6 to 42)
Psychoeducation group + AD	27	-0.47 (-2.05 to 1.04)	26.47 (5 to 43)
CT/CBT group	165	-0.48 (-1.73 to 0.71)	26.51 (6 to 42)
Mirtazapine	1,884	**-0.45 (-0.59 to -0.32)**	27.12 (21 to 34)
TCAs	4,524	**-0.43 (-0.60 to -0.24)**	27.80 (21 to 35)
Exercise group	106	-0.42 (-1.24 to 0.42)	27.84 (11 to 41)
SNRIs	9,538	**-0.43 (-0.54 to -0.32)**	27.95 (22 to 34)
Exercise individual	298	-0.32 (-1.59 to 1.01)	29.69 (7 to 43)
Counselling individual + AD	57	-0.16 (-2.18 to 1.87)	30.10 (4 to 43)
SSRIs	22,018	**-0.33 (-0.40 to -0.26)**	31.28 (26 to 36)
TAU	220	-0.22 (-0.57 to 0.13)	33.39 (24 to 40)
Sham acupuncture	108	-0.08 (-1.01 to 0.79)	34.18 (15 to 43)
Trazodone	1,072	-0.18 (-0.37 to 0.01)	34.47 (28 to 39)
Placebo	12,554	Reference	37.72 (33 to 41)
Attention placebo	61	0.21 (-0.57 to 1.01)	38.36 (25 to 43)
Waitlist	526	0.63 (0.26 to 1.00)	41.97 (39 to 43)

Treatment classes ordered from best to worst, according to mean ranking. Negative effect values indicate a favourable outcome for treatment classes compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

The base-case relative effects (posterior mean SMD with 95% CrI) of all individual interventions versus pill placebo (reference treatment for more severe depression) are reported in Table 19. Interventions have been listed by treatment class.

Table 19. Base-case results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression: posterior effects (mean SMD, 95%CrI) of all interventions versus pill placebo. Only interventions of interest belonging to classes with N ≥50 have been included in the table.

Treatment class	N	SMD vs pill placebo (mean, 95% CrI)	Intervention	N	SMD vs pill placebo (mean, 95% CrI)
Self-help without/with minimal support	344	-1.21 (-3.43 to 0.89)	**Cognitive bibliotherapy**	**159**	**-1.04 (-1.56 to -0.53)**
			Computerised-CBT (CCBT)	**120**	**-0.64 (-1.17 to -0.11)**
			Computerised attentional bias modification	26	-0.54 (-1.67 to 0.66)
			Mindfulness meditation CD	**39**	**-2.65 (-4.29 to -0.93)**
Self-help with support	267	-0.70 (-1.51 to 0.13)	**Cognitive bibliotherapy with support**	**66**	**-0.70 (-1.24 to -0.16)**
			Computerised-CBT (CCBT) with support	**164**	**-0.71 (-1.11 to -0.31)**
			Mindfulness meditation CD with support	19	-0.63 (-1.73 to 0.60)
			Relaxation training CD with support	18	-0.81 (-2.14 to 0.21)
Behavioural therapies individual	**378**	**-1.01 (-1.98 to -0.08)**	**Behavioural activation (BA) individual**	**368**	**-0.83 (-1.31 to -0.34)**
			Behavioural therapy (Lewinsohn 1976) individual	**10**	**-1.19 (-2.02 to -0.41)**
CT/CBT individual	**1,044**	**-1.00 (-1.71 to -0.38)**	**CBT individual (15 sessions or over)**	**626**	**-0.69 (-0.95 to -0.43)**
			CBT individual (under 15 sessions)	**369**	**-0.78 (-1.10 to -0.46)**
			Dialectical behavioural therapy (DBT) individual	**10**	**-1.59 (-2.59 to -0.72)**
			Third-wave cognitive therapy individual	**39**	**-0.93 (-1.50 to -0.38)**
CT/CBT group	165	-0.48 (-1.73 to 0.71)	**CBT group (under 15 sessions)**	**165**	**-0.48 (-0.88 to -0.09)**
Problem solving individual	367	-0.79 (-2.04 to 0.44)	**Problem solving individual**	**367**	**-0.79 (-1.23 to -0.34)**
Counselling individual	404	-0.55 (-1.78 to 0.68)	**Non-directive/supportive/person-centred counselling**	**404**	**-0.55 (-0.93 to -0.17)**
IPT individual	146	-0.52 (-1.77 to 0.72)	**IPT individual**	**146**	**-0.52 (-0.99 to -0.05)**
Short-term PDPT individual	233	-0.86 (-1.82 to 0.05)	**Dynamic interpersonal therapy (DIT) individual**	**73**	**-1.17 (-1.93 to -0.47)**
			Short-term psychodynamic psychotherapy individual	**160**	**-0.55 (-1.01 to -0.09)**
SSRIs	**22,018**	**-0.33 (-0.40 to -0.26)**	**Citalopram**	**2,195**	**-0.32 (-0.40 to -0.22)**
			Escitalopram	**4,930**	**-0.36 (-0.45 to -0.28)**

			Fluoxetine	**6,031**	**-0.31 (-0.38 to -0.23)**
			Paroxetine	**5,861**	**-0.33 (-0.40 to -0.26)**
			Sertraline	**2,794**	**-0.33 (-0.41 to -0.25)**
TCAs	**4,524**	**-0.43 (-0.60 to -0.24)**	**Amitriptyline**	**2,462**	**-0.49 (-0.61 to -0.39)**
			Clomipramine	**345**	**-0.42 (-0.61 to -0.21)**
			Imipramine	**1,306**	**-0.41 (-0.54 to -0.26)**
			Lofepramine	**145**	**-0.46 (-0.71 to -0.25)**
			Nortriptyline	**245**	**-0.38 (-0.56 to -0.13)**
SNRIs	**9,538**	**-0.43 (-0.54 to -0.32)**	**Duloxetine**	**5,269**	**-0.43 (-0.52 to -0.34)**
			Venlafaxine	**4,269**	**-0.43 (-0.52 to -0.34)**
Mirtazapine	**1,884**	**-0.46 (-0.59 to -0.32)**	**Mirtazapine**	**1,884**	**-0.46 (-0.59 to -0.32)**
Trazodone	**1,072**	**-0.18 (-0.37 to 0.01)**	**Trazodone**	**1,072**	**-0.18 (-0.37 to 0.01)**
Acupuncture	264	-0.56 (-1.42 to 0.23)	**Electroacupuncture**	**110**	**-0.56 (-1.02 to -0.10)**
			Laser acupuncture	39	-0.93 (-2.14 to 0.11)
			Traditional acupuncture	115	-0.19 (-0.63 to 0.25)
Exercise individual	298	-0.32 (-1.59 to 1.01)	Supervised high intensity exercise individual	128	-0.42 (-0.93 to 0.10)
			Supervised low intensity exercise individual	117	-0.17 (-0.80 to 0.56)
			Unsupervised high intensity exercise individual	53	-0.36 (-0.84 to 0.13)
Exercise group	106	-0.42 (-1.24 to 0.42)	**Supervised high intensity exercise group**	**69**	**-0.47 (-0.92 to -0.03)**
			Supervised low intensity exercise group	37	-0.38 (-0.91 to 0.21)
Yoga group	65	-0.97 (-2.34 to 0.38)	**Yoga group**	**65**	**-0.98 (-1.71 to -0.24)**
CT/CBT individual + AD	**192**	**-1.25 (-1.97 to -0.62)**	**CBT individual (15 sessions or over) + any AD**	**10**	**-1.47 (-2.49 to -0.61)**
			CBT individual (15 sessions or over) + any SSRI	**43**	**-0.84 (-1.35 to -0.31)**
			CBT individual (15 sessions or over) + imipramine	**25**	**-1.18 (-1.99 to -0.40)**
			CBT individual (15 sessions or over) + nortriptyline	**18**	**-0.95 (-1.75 to -0.13)**
			CBT individual (under 15 sessions) + escitalopram	**48**	**-0.71 (-1.28 to -0.10)**
			CBT individual (under 15 sessions) + sertraline	**38**	**-1.43 (-2.74 to -0.31)**
			Third-wave cognitive therapy individual + any AD	**10**	**-2.16 (-3.24 to -1.10)**
CT/CBT group + AD	121	-1.27 (-2.80 to 0.19)	**CBT group (under 15 sessions) + any AD**	**63**	**-1.27 (-1.90 to -0.64)**

IPT individual + AD	99	-0.81 (-1.96 to 0.29)	**IPT individual + any AD**	**87**	**-0.80 (-1.38 to -0.23)**
			Interpersonal counselling individual + venlafaxine	12	-0.84 (-1.76 to 0.05)
Counselling individual + AD	57	-0.16 (-2.18 to 1.87)	Non-directive/supportive/person-centred counselling + any AD	15	-0.17 (-2.17 to 1.79)
			Non-directive/supportive/person-centred counselling + any SSRI	17	-0.25 (-2.24 to 1.64)
			Non-directive/supportive/person-centred counselling + fluoxetine	25	-0.22 (-2.70 to 2.19)
Short-term PDPT individual + AD	131	-0.51 (-2.10 to 1.06)	Short-term psychodynamic psychotherapy individual + any AD	113	-0.57 (-1.64 to 0.50)
			Short-term psychodynamic psychotherapy individual + any SSRI	18	-0.50 (-2.41 to 1.31)
Exercise group + AD	**79**	**-1.46 (-2.69 to -0.22)**	**Supervised high intensity exercise group + sertraline**	**42**	**-1.59 (-2.44 to -0.75)**
			Supervised low intensity exercise group + sertraline	**37**	**-1.32 (-2.20 to -0.44)**
Acupuncture + AD	**584**	**-0.87 (-1.22 to -0.51)**	**Electroacupuncture + any SSRI**	**160**	**-0.90 (-1.30 to -0.54)**
			Electroacupuncture + fluoxetine	**46**	**-0.83 (-1.23 to -0.35)**
			Electroacupuncture + paroxetine	**71**	**-0.93 (-1.31 to -0.59)**
			Traditional acupuncture + any SSRI	**206**	**-0.83 (-1.16 to -0.47)**
			Traditional acupuncture + paroxetine	**101**	**-0.86 (-1.20 to -0.51)**
Light therapy + AD	**54**	**-0.99 (-1.92 to -0.04)**	**Bright light therapy + fluoxetine**	**29**	**-1.11 (-1.70 to -0.53)**
			Bright light therapy + venlafaxine	**25**	**-0.86 (-1.53 to -0.19)**

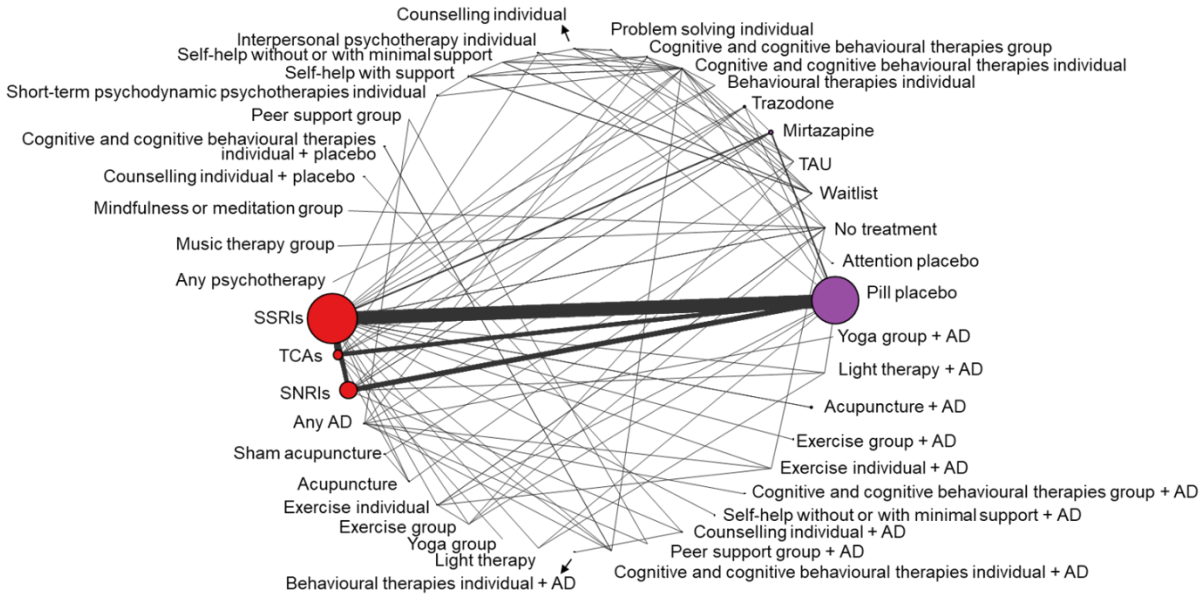
Negative effect values indicate a favourable outcome for treatment classes and interventions compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Response in those randomised

The network plot at the treatment class level is shown in Figure 11. The number of participants tested on each treatment class and each intervention are shown in Table 20. The base-case relative effects (posterior mean log-odds ratio [LOR] with 95% CrI) of all treatment classes versus pill placebo (reference treatment for more severe depression) are illustrated in Figure 12 (forest plots) and reported in Table 21.

Table 21 The same table shows also the class treatment rankings. Treatment classes in the table have been ordered from lowest to highest ranking (with lower rankings suggesting greater effects).

Figure 11. Network plot of the NMA of response in those randomised in adults with a new episode of more severe depression – treatment class level



The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 20. Treatment classes, interventions and numbers of participants tested on each in the NMA of response in those randomised in adults with a new episode of more severe depression

Treatment class	N	Intervention	N
Pill placebo	15,384	Pill placebo	15,384
Attention placebo	36	Attention placebo	36
No treatment	441	No treatment	441
Waitlist	349	Waitlist	349
TAU	176	TAU	176
Sham acupuncture	74	Inactive laser acupuncture	22
		Traditional non-specific point acupuncture	52
Self-help without or with minimal support	168	Cognitive bibliotherapy	32
		Computerised-CBT (CCBT)	97
		Mindfulness meditation CD	39
Self-help with support	274	Cognitive bibliotherapy with support	66
		Computerised-CBT (CCBT) with support	208
Behavioural therapies individual	368	Behavioural activation (BA) individual	368
CT/CBT individual	779	CBT individual (15 sessions or over)	470
		CBT individual (under 15 sessions)	260
		Dialectical behavioural therapy (DBT) individual	10
		Third-wave cognitive therapy individual	39
CT/CBT group	155	CBT group (under 15 sessions)	155
Problem solving individual	338	Problem solving individual	338
Counselling individual	421	Non-directive/supportive/person-centred counselling	421
IPT individual	61	IPT individual	61

Short-term PDPT individual	217	Dynamic interpersonal therapy (DIT) individual	73
		Short-term PDPT individual	144
Music therapy group	12	Music therapy group	12
Mindfulness or meditation group	15	MBCT group	15
Peer support group	39	Peer support group	39
Any psychotherapy	22	Any psychotherapy	22
CT/CBT + pill placebo	58	CBT individual (15 sessions or over) + pill placebo	14
		CBT individual (under 15 sessions) + pill placebo	44
Counselling individual + pill placebo	26	Non-directive/supportive/person-centred counselling + pill placebo	26
SSRIs	26,961	Any SSRI	156
		Citalopram	3,242
		Escitalopram	5,863
		Fluoxetine	7,732
		Paroxetine	6,661
		Sertraline	3,307
TCAs	54,37	Amitriptyline	2,519
		Clomipramine	414
		Imipramine	2,061
		Lofepramine	242
		Nortriptyline	201
SNRIs	10,469	Duloxetine	5,472
		Venlafaxine	4,997
Mirtazapine	2,629	Mirtazapine	2,629
Trazodone	1,181	Trazodone	1,181
Any AD	188	Any AD	188
Acupuncture	217	Electroacupuncture	77
		Laser acupuncture	25
		Traditional acupuncture	115
Exercise individual	273	Supervised high intensity exercise individual	114
		Supervised low intensity exercise individual	106
		Unsupervised high intensity exercise individual	53
Exercise group	126	Supervised high intensity exercise group	106
		Supervised low intensity exercise group	20
Yoga group	45	Yoga group	45
Light therapy	32	Bright light therapy	32
Behavioural therapies individual + AD	10	Behavioural activation (BA) individual + any AD	10
CT/CBT individual + AD	158	CBT individual (15 sessions or over) + amitriptyline	12
		CBT individual (15 sessions or over) + any AD	10
		CBT individual (15 sessions or over) + imipramine	25
		CBT individual (15 sessions or over) + trazodone	11
		CBT individual (under 15 sessions) + escitalopram	52
		CBT individual (under 15 sessions) + sertraline	38
		Third-wave cognitive therapy individual + any AD	10
CT/CBT + AD	20	CBT group (under 15 sessions) + any AD	20
Counselling individual + AD	52	Interpersonal counselling individual + venlafaxine	12
		Non-directive/supportive/person-centred counselling + any AD	15
		Non-directive/supportive/person-centred counselling + fluoxetine	25
Self-help + AD	79	Cognitive bibliotherapy + escitalopram	79
Peer support group + AD	42	Peer support group + any AD	42

Exercise individual + AD	40	Supervised high intensity exercise individual + any AD	14
		Supervised high intensity exercise individual + sertraline	15
		Supervised low intensity exercise individual + any AD	11
Exercise group + AD	79	Supervised high intensity exercise group + sertraline	42
		Supervised low intensity exercise group + sertraline	37
Yoga group + AD	15	Yoga group + any AD	15
Acupuncture + AD	553	Electroacupuncture + any SSRI	160
		Electroacupuncture + fluoxetine	48
		Electroacupuncture + paroxetine	80
		Traditional acupuncture + any SSRI	161
		Traditional acupuncture + paroxetine	104
Light therapy + AD	54	Bright light therapy + fluoxetine	29
		Bright light therapy + venlafaxine	25

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Figure 12. Forest plots of response in those randomised in adults with a new episode of more severe depression: effects of treatment classes versus pill placebo (N=15,384) Values on the right side of the vertical axis indicate better effect compared with pill placebo. Results are expressed as log-odds ratios (LORs). Effects are shown only for treatment classes with N ≥ 50.

AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 21. Base-case results of the NMA of response in those randomised in adults with a new episode of more severe depression: posterior effects (mean log-odds ratio [LOR], 95%CrI) of all treatment classes versus pill placebo and treatment class rankings

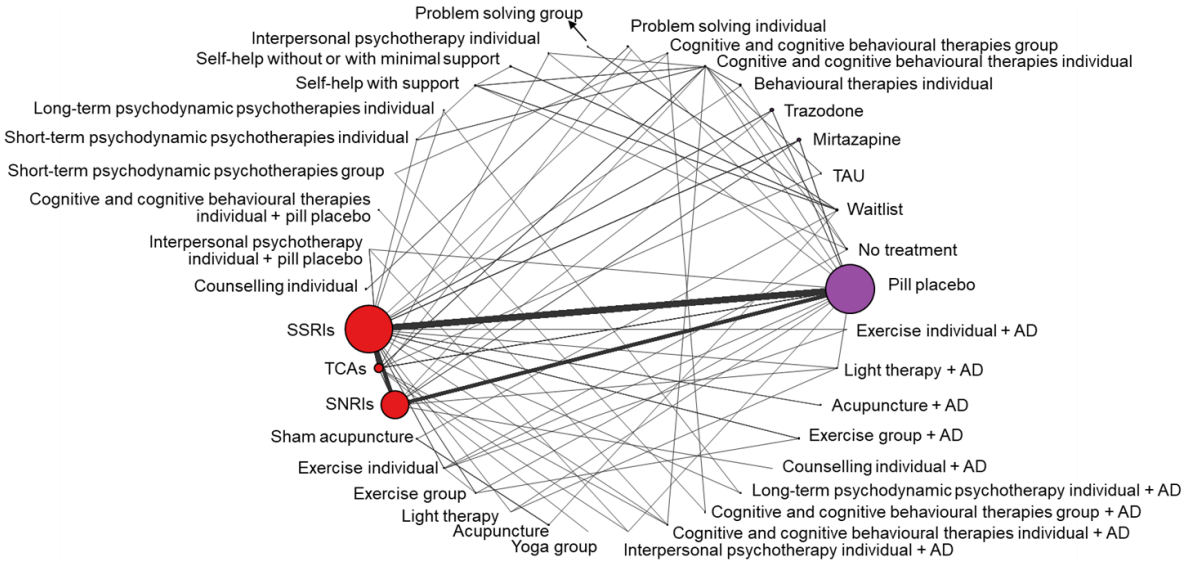
Treatment class	N	LOR vs pill placebo (mean, 95% CrI)	Rank (mean, 95% CrI)
Mindfulness or meditation group	15	**6.61 (4.03 to 9.19)**	1.48 (1 to 4)
Yoga group + AD	15	3.68 (-0.07 to 7.63)	6.91 (1 to 32)
Exercise individual + AD	40	**2.86 (0.58 to 5.23)**	8.25 (2 to 25)
CT/CBT individual + AD	158	**2.73 (0.86 to 4.72)**	8.39 (2 to 21)
Peer support group	39	**2.71 (0.28 to 5.21)**	9.03 (2 to 29)
Peer support group + AD	42	2.91 (-0.66 to 6.66)	9.64 (1 to 35)
Exercise group + AD	79	2.56 (-0.14 to 5.28)	10.21 (2 to 33)
CT/CBT group + AD	20	2.78 (-0.83 to 6.55)	10.36 (2 to 36)
Behavioural therapies individual + AD	10	2.86 (-3.78 to 9.24)	12.55 (1 to 38)
CT/CBT individual	779	**1.69 (0.63 to 3.02)**	13.92 (6 to 24)
Light therapy + AD	54	1.79 (-0.97 to 4.55)	14.44 (3 to 36)
Behavioural therapies individual	368	1.68 (-0.55 to 3.89)	14.87 (4 to 35)
Self-help	168	1.61 (-0.30 to 3.55)	15.07 (4 to 34)
Short-term PDPT individual	217	1.48 (-0.09 to 3.20)	16.16 (5 to 32)
Acupuncture + AD	553	**1.36 (0.76 to 1.95)**	16.29 (10 to 23)
Self-help with support	274	1.34 (-0.25 to 3.01)	17.34 (6 to 33)
Counselling individual + AD	52	1.46 (-2.47 to 5.26)	17.97 (3 to 38)
IPT individual	61	1.21 (-1.09 to 3.53)	18.9 (5 to 36)
Problem solving individual	338	1.15 (-0.99 to 3.39)	19.43 (5 to 36)
Light therapy	32	1.05 (-2.78 to 4.92)	20.52 (2 to 38)
Music therapy group	12	0.92 (-1.70 to 3.59)	21.57 (5 to 38)
Counselling individual	421	0.86 (-1.29 to 3.10)	22.14 (6 to 37)
Self-help + AD	79	0.80 (-2.72 to 4.37)	22.42 (3 to 38)
Mirtazapine	2629	**0.72 (0.56 to 0.88)**	22.98 (18 to 28)
Yoga group	45	0.69 (-2.12 to 3.47)	23.32 (5 to 38)
TCAs	5437	**0.70 (0.43 to 1.00)**	23.45 (18 to 29)
SNRIs	10469	**0.66 (0.53 to 0.79)**	24.03 (19 to 29)
CT/CBT group	155	0.63 (-1.50 to 2.89)	24.44 (7 to 37)
Acupuncture	217	0.59 (-1.91 to 3.15)	24.51 (6 to 38)
Exercise individual	273	0.59 (-1.05 to 2.17)	24.77 (10 to 37)
Exercise group	126	0.47 (-1.27 to 2.06)	25.93 (11 to 37)
SSRIs	26961	**0.54 (0.45 to 0.63)**	26.53 (22 to 31)
Trazodone	1181	**0.36 (0.13 to 0.59)**	28.71 (24 to 33)
Sham acupuncture	74	-0.29 (-3.62 to 2.91)	30.33 (7 to 38)
TAU	176	0.08 (-0.64 to 0.79)	30.90 (23 to 36)
Pill placebo	15384	Reference	32.04 (28 to 36)
Attention placebo	36	-0.76 (-2.05 to 0.54)	35.03 (27 to 38)
Waitlist	349	**-0.93 (-1.61 to -0.25)**	36.17 (33 to 38)

Treatment classes ordered from best to worst, according to mean ranking. Positive effect values indicate a favourable outcome for treatment classes compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; LOR: log-odds ratio; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Remission in those randomised

The network plot at the treatment class level is shown in Figure 13. The number of participants tested on each treatment class and each intervention are shown in Table 22. The base-case relative effects (posterior mean log-odds ratio [LOR] with 95% CrI) of all treatment classes versus pill placebo (reference treatment for more severe depression) are illustrated in Figure 14 (forest plots) and reported in Table 23. The same table shows also the class treatment rankings. Treatment classes in the table have been ordered from lowest to highest ranking (with lower rankings suggesting greater effects).

Figure 13. Network plot of the NMA of remission in those randomised in adults with a new episode of more severe depression – treatment class level



The width of lines is proportional to the number of trials that make each direct comparison; the size of each circle (treatment node) is proportional to the number of participants tested on each treatment class.
AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

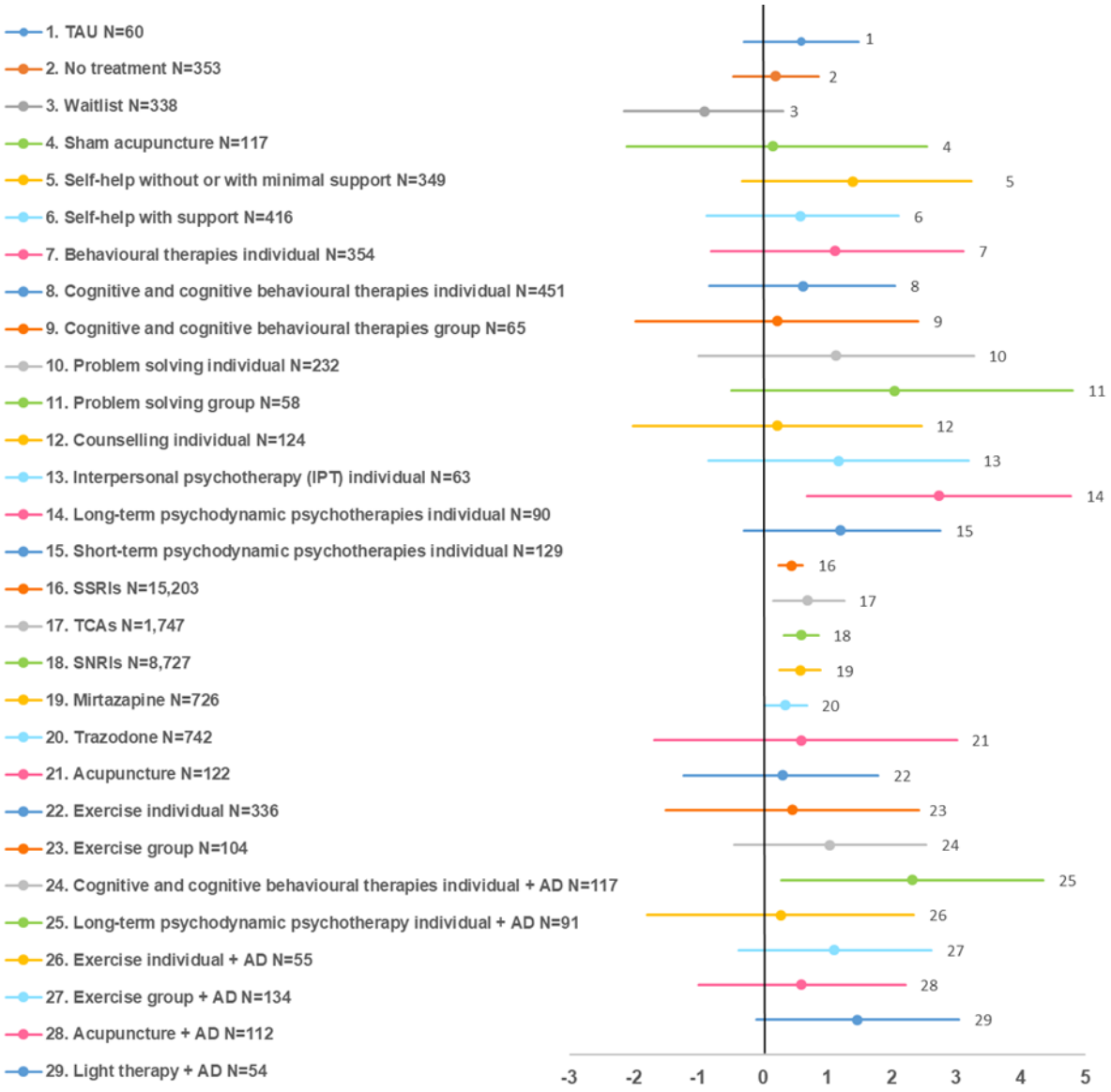
Table 22. Treatment classes, interventions and numbers of participants tested on each in the NMA of remission in those randomised in adults with a new episode of more severe depression

Treatment class	N	Intervention	N
Pill placebo	8,376	Pill placebo	8,376
No treatment	353	No treatment	353
Waitlist	338	Waitlist	338
TAU	60	TAU	60
Sham acupuncture	117	Inactive laser acupuncture	36
		Sham electrostimulation at non-specific points with no current	29
		Traditional non-specific point acupuncture	52
Self-help without or with minimal support	349	Cognitive bibliotherapy	156
		Mindfulness meditation CD	39
		Psychoeducational website	154
Self-help with support	416	Cognitive bibliotherapy with support	54
		Computerised-CBT (CCBT) with support	203
		Computerised behavioural activation with support	159
Behavioural therapies individual	354	Behavioural activation (BA) individual	354
CT/CBT individual	451	CBT individual (15 sessions or over)	421
		CBT individual (under 15 sessions)	30

CT/CBT group	65	CBT group (under 15 sessions)	65
Problem solving individual	232	Problem solving individual	232
Problem solving group	58	Problem solving group	58
Counselling individual	124	Non-directive/supportive/person-centred counselling	124
IPT individual	63	IPT individual	63
Long-term PDPT individual	90	Long-term PDPT individual	90
Short-term PDPT individual	129	Dynamic interpersonal therapy (DIT) individual	73
		Short-term PDPT individual	56
Short-term PDPT group	24	Short-term PDPT group	24
CT/CBT individual + pill placebo	39	CBT individual (under 15 sessions) + pill placebo	39
IPT individual + pill placebo	48	IPT individual + pill placebo	48
SSRIs	15,203	Citalopram	1,676
		Escitalopram	3,818
		Fluoxetine	3,981
		Paroxetine	4,571
		Sertraline	1,157
TCAs	1,747	Amitriptyline	666
		Clomipramine	184
		Imipramine	562
		Lofepramine	68
		Nortriptyline	267
SNRIs	8,727	Duloxetine	5,472
		Venlafaxine	3,255
Mirtazapine	726	Mirtazapine	726
Trazodone	742	Trazodone	742
Acupuncture	122	Electroacupuncture	28
		Laser acupuncture	41
		Traditional acupuncture	53
Exercise individual	336	Supervised high intensity exercise individual	177
		Supervised low intensity exercise individual	106
		Unsupervised high intensity exercise individual	53
Exercise group	104	Supervised high intensity exercise group	104
Yoga group	15	Yoga group	15
Light therapy	32	Bright light therapy	32
CT/CBT individual + AD	117	CBT individual (15 sessions or over) + imipramine	25
		CBT individual (under 15 sessions) + escitalopram	52
		CBT individual (under 15 sessions) + sertraline	40
CT/CBT group + AD	34	CBT group (under 15 sessions) + imipramine	34
Long-term PDPT + AD	91	Long-term PDPT individual + fluoxetine	91
IPT individual + AD	16	IPT individual + nortriptyline	16
Counselling individual + AD	13	Interpersonal counselling individual + venlafaxine	13
Exercise individual + AD	55	Supervised high intensity exercise individual + sertraline	55
Exercise group + AD	134	Supervised high intensity exercise group + sertraline	97
		Supervised low intensity exercise group + sertraline	37
Acupuncture + AD	112	Electroacupuncture + paroxetine	58
		Traditional acupuncture + paroxetine	54
Light therapy + AD	54	Bright light therapy + fluoxetine	29
		Bright light therapy + venlafaxine	25

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Figure 14. Forest plots of remission in those randomised in adults with a new episode of more severe depression: effects of treatment classes versus pill placebo (N=8,376) Values on the right side of the vertical axis indicate better effect compared with pill placebo. Only classes with N ≥ 50 are shown.



AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 23. Base-case results of the NMA of remission in those randomised in adults with a new episode of more severe depression: posterior effects (mean log-odds ratio [LOR], 95%CrI) of all treatment classes versus pill placebo and treatment class rankings

Treatment class	N	LOR vs pill placebo (mean, 95% CrI)	Rank (mean, 95% CrI)
Long-term PDPT individual	90	**2.73 (0.69 to 4.78)**	3.87 (1 to 17)
Long-term PDPT individual + AD	91	**2.32 (0.29 to 4.35)**	5.54 (1 to 24)
Problem solving group	58	2.05 (-0.49 to 4.81)	8.18 (1 to 31)
Light therapy + AD	54	1.47 (-0.10 to 3.04)	10.09 (2 to 28)
IPT individual + AD	16	1.54 (-0.72 to 3.84)	11.00 (1 to 32)
Self-help without/with minimal support	349	1.39 (-0.32 to 3.24)	11.28 (2 to 29)
Short-term PDPT individual	129	1.21 (-0.29 to 2.76)	12.50 (2 to 30)
Exercise group + AD	134	1.11 (-0.38 to 2.62)	13.42 (3 to 30)
IPT individual	63	1.17 (-0.84 to 3.19)	13.48 (2 to 32)
Behavioural therapies individual	354	1.12 (-0.80 to 3.11)	13.84 (2 to 32)
Problem solving individual	232	1.13 (-0.99 to 3.27)	13.96 (2 to 33)
CT/CBT individual + AD	117	1.04 (-0.44 to 2.53)	14.17 (3 to 31)
Light therapy	32	1.05 (-1.06 to 3.18)	14.77 (2 to 33)
Counselling individual + AD	13	0.88 (-1.53 to 3.29)	16.43 (1 to 34)
TCAs	1,747	**0.70 (0.16 to 1.26)**	17.28 (9 to 27)
Acupuncture	122	0.60 (-1.68 to 3.01)	18.64 (2 to 33)
SNRIs	8,727	**0.60 (0.33 to 0.86)**	18.76 (12 to 25)
CT/CBT individual	451	0.62 (-0.83 to 2.05)	18.84 (5 to 32)
TAU	60	0.60 (-0.29 to 1.49)	19.14 (8 to 31)
Mirtazapine	726	**0.58 (0.26 to 0.90)**	19.15 (12 to 26)
Acupuncture + AD	112	0.60 (-0.99 to 2.21)	19.19 (4 to 33)
Self-help with support	416	0.58 (-0.87 to 2.10)	19.56 (5 to 32)
Exercise group	104	0.46 (-1.50 to 2.42)	20.59 (4 to 34)
SSRIs	15,203	**0.44 (0.25 to 0.62)**	21.81 (16 to 27)
Exercise individual + AD	55	0.28 (-1.79 to 2.34)	22.13 (4 to 34)
CT/CBT group	65	0.23 (-1.97 to 2.41)	22.30 (4 to 34)
Counselling individual	124	0.22 (-2.01 to 2.46)	22.35 (4 to 34)
Yoga group	15	0.17 (-2.39 to 2.72)	22.36 (3 to 35)
Sham acupuncture	117	0.16 (-2.11 to 2.55)	22.55 (4 to 34)
Exercise individual	336	0.31 (-1.23 to 1.79)	22.69 (6 to 33)
CT/CBT group + AD	34	0.12 (-2.32 to 2.57)	22.90 (3 to 34)
Trazodone	742	**0.35 (0.03 to 0.68)**	23.11 (16 to 29)
Pill placebo	8376	Reference	27.78 (23 to 32)
Waitlist	338	-0.91 (-2.15 to 0.32)	32.01 (25 to 35)
Short-term PDPT group	24	**-3.22 (-7.00 to -0.06)**	34.32 (28 to 35)

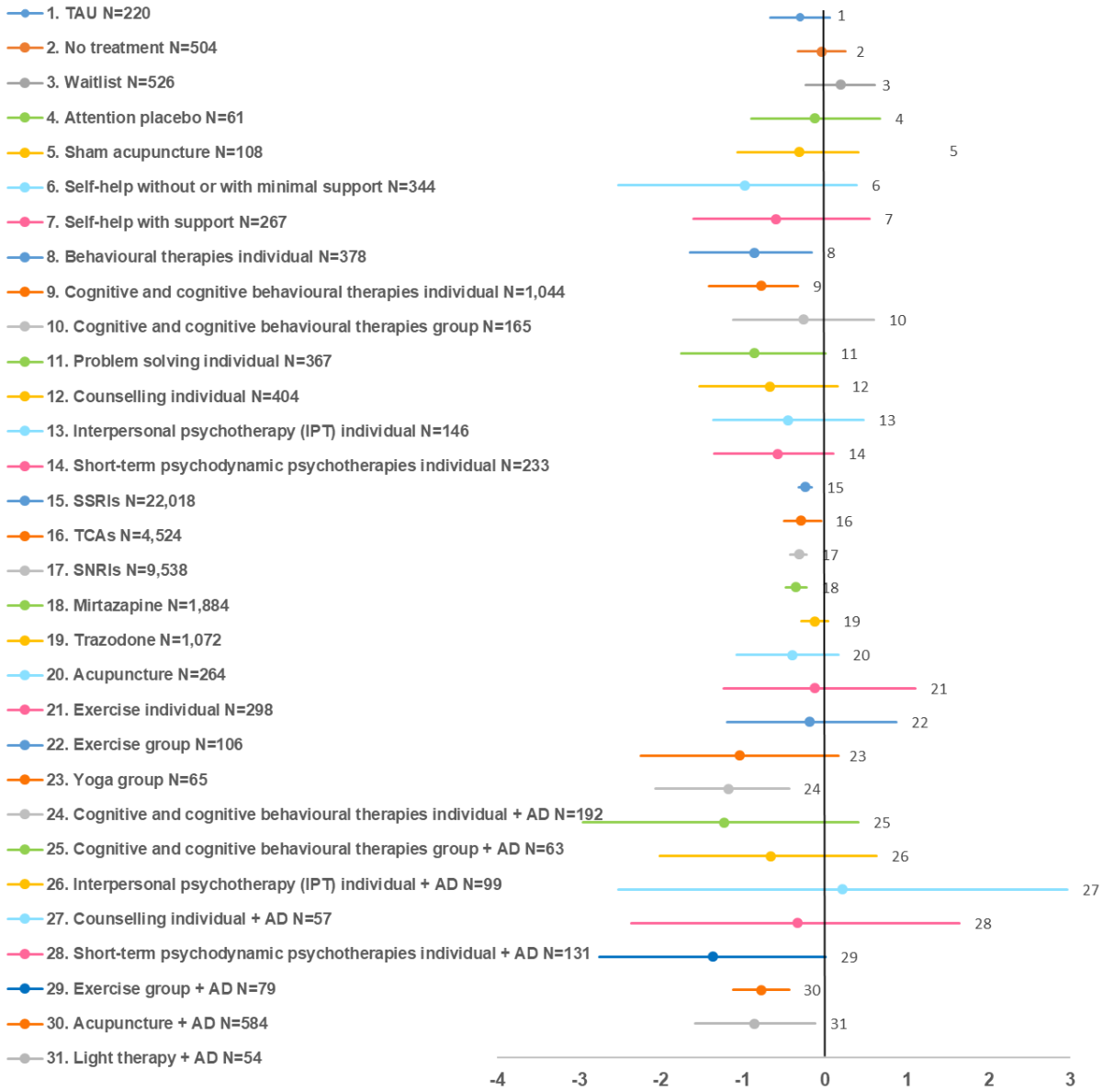
Treatment classes ordered from best to worst, according to mean ranking. Positive effect values indicate a favourable outcome for treatment classes compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; LOR: log-odds ratio; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Bias-adjusted analysis

Bias models tested on the SMD outcome suggested evidence of bias due to small study size.

Figure 15 shows the bias-adjusted forest plots of relative effects (posterior mean SMD with 95% CrI) of all treatment classes versus pill placebo (reference treatment for more severe depression). Table 24 shows the relative effects of all treatment classes versus pill placebo on the SMD and the class treatment rankings. Treatment classes in the table have been ranked from lowest to highest ranking (with lower rankings suggesting greater effects). Table 25 shows the bias-adjusted relative effects (posterior mean SMD with 95% CrI) of all individual interventions versus pill placebo (reference treatment for more severe depression). Interventions in this table have been listed by treatment class.

Figure 15. Bias-adjusted forest plots of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression: effects of treatment classes versus pill placebo (N=12,554). Values on the left side of the vertical axis indicate better effect compared with pill placebo. Effects are shown only for treatment classes with N ≥ 50.



AD: antidepressant; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 24. Bias-adjusted results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression: posterior effects (mean SMD, 95%CrI) of all treatment classes versus pill placebo and treatment class rankings

Treatment class	N	SMD vs pill placebo (mean, 95% CrI)	Rank (mean, 95% CrI)
Mindfulness or meditation group	15	**-3.40 (-4.77 to -2.03)**	1.41 (1 to 4)
Problem solving group	47	**-2.29 (-3.49 to -1.10)**	3.76 (1 to 12)
Yoga group + AD	15	-1.89 (-3.95 to 0.10)	7.82 (1 to 38)
Peer support group	39	**-1.35 (-2.42 to -0.26)**	9.83 (3 to 30)
Peer support group + AD	42	-1.47 (-3.30 to 0.25)	10.42 (2 to 39)
Exercise group + AD	79	-1.37 (-2.75 to 0.01)	10.63 (2 to 37)
CT/CBT individual + AD	192	**-1.18 (-2.07 to -0.44)**	11.09 (4 to 24)
CT/CBT group + AD	63	-1.23 (-2.95 to 0.41)	12.86 (2 to 40)
Psychoeducation group	44	-1.01 (-2.06 to 0.00)	14.18 (3 to 36)
Yoga group	65	-1.04 (-2.25 to 0.17)	14.26 (3 to 39)
Self-help without/with minimal support	344	-0.98 (-2.52 to 0.39)	14.99 (3 to 41)
Behavioural therapies individual	378	**-0.86 (-1.65 to -0.16)**	15.97 (5 to 33)
Exercise individual + AD	40	-0.96 (-2.25 to 0.27)	15.98 (3 to 40)
Light therapy + AD	54	**-0.86 (-1.59 to -0.12)**	16.07 (5 to 34)
Problem solving individual	367	-0.86 (-1.75 to 0.01)	16.22 (5 to 36)
Acupuncture + AD	584	**-0.78 (-1.12 to -0.44)**	16.88 (9 to 26)
CT/CBT individual	1,044	**-0.78 (-1.42 to -0.33)**	17.28 (8 to 27)
Counselling individual	404	-0.67 (-1.53 to 0.15)	19.96 (7 to 39)
Light therapy	32	-0.64 (-1.60 to 0.29)	20.89 (6 to 40)
Self-help with support	267	-0.60 (-1.61 to 0.54)	21.32 (6 to 41)
IPT individual + AD	99	-0.66 (-2.02 to 0.63)	21.32 (4 to 42)
Short-term PDPT individual	233	-0.58 (-1.35 to 0.10)	22.08 (8 to 38)
IPT individual	146	-0.45 (-1.36 to 0.47)	25.01 (8 to 41)
Acupuncture	264	-0.40 (-1.08 to 0.16)	26.35 (12 to 39)
Short-term PDPT individual + AD	131	-0.34 (-2.36 to 1.64)	26.51 (3 to 43)
Psychoeducation group + AD	27	-0.35 (-2.13 to 1.35)	26.59 (4 to 43)
Mirtazapine	1,884	**-0.35 (-0.48 to -0.22)**	27.04 (20 to 34)
Behavioural therapies individual + AD	22	-0.13 (-2.82 to 2.71)	28.06 (2 to 43)
SNRIs	9,538	**-0.32 (-0.43 to -0.22)**	28.07 (22 to 34)
Sham acupuncture	108	-0.31 (-1.07 to 0.41)	28.47 (12 to 41)
TAU	220	-0.30 (-0.67 to 0.06)	28.96 (19 to 38)
Relaxation individual + AD	10	0.05 (-2.82 to 2.96)	29.23 (2 to 43)
TCAs	4,524	**-0.29 (-0.50 to -0.05)**	29.34 (21 to 37)
Music therapy group	12	-0.14 (-1.69 to 1.41)	29.54 (5 to 43)
CT/CBT group	165	-0.26 (-1.12 to 0.60)	29.59 (11 to 42)
Exercise group	106	-0.19 (-1.20 to 0.87)	30.60 (10 to 42)
SSRIs	22,018	**-0.24 (-0.32 to -0.16)**	31.21 (25 to 37)
Exercise individual	298	-0.13 (-1.24 to 1.10)	31.75 (9 to 43)
Counselling individual + AD	57	0.21 (-2.52 to 2.96)	32.21 (4 to 43)
Attention placebo	61	-0.12 (-0.90 to 0.67)	32.27 (15 to 42)
Trazodone	1,072	-0.13 (-0.29 to 0.04)	34.14 (27 to 40)
Placebo	12,554	Reference	37.00 (32 to 41)
Waitlist	526	0.19 (-0.24 to 0.61)	38.83 (31 to 43)

Treatment classes ordered from best to worst, according to mean ranking. Negative effect values indicate a favourable outcome for treatment classes compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Table 25. Bias-adjusted results of the NMA of standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression: posterior effects (mean SMD, 95%CrI) of all interventions versus pill placebo. Only interventions of interest belonging to classes with N ≥50 have been included in the table.

Class	N	SMD vs pill placebo (mean, 95% CrI)	Intervention	N	SMD vs pill placebo (mean, 95% CrI)
Self-help without/with minimal support	344	-0.98 (-2.52 to 0.39)	**Cognitive bibliotherapy**	**159**	**-1.15 (-1.74 to -0.59)**
			Computerised-CBT (CCBT)	**120**	**-0.79 (-1.32 to -0.25)**
			Computerised attentional bias modification	26	-0.63 (-1.64 to 0.70)
			Mindfulness meditation CD	39	**-1.40 (-3.57 to -0.03)**
Self-help with support	267	-0.60 (-1.61 to 0.54)	Cognitive bibliotherapy with support	66	-0.54 (-1.24 to 0.30)
			Computerised-CBT (CCBT) with support	**164**	**-0.68 (-1.13 to -0.23)**
			Mindfulness meditation CD with support	19	-0.53 (-1.86 to 1.06)
			Relaxation training CD with support	18	-0.71 (-2.23 to 0.65)
Behavioural therapies individual	**378**	**-0.86 (-1.65 to -0.16)**	**Behavioural activation (BA) individual**	**368**	**-0.77 (-1.26 to -0.28)**
			Behavioural therapy (Lewinsohn 1976) individual	**10**	**-0.96 (-1.83 to -0.25)**
CT/CBT individual	**1,044**	**-0.78 (-1.42 to -0.33)**	**CBT individual (15 sessions or over)**	**626**	**-0.60 (-0.90 to -0.30)**
			CBT individual (under 15 sessions)	**369**	**-0.73 (-1.08 to -0.41)**
			Dialectical behavioural therapy (DBT) individual	**10**	**-0.99 (-2.31 to -0.31)**
			Third-wave cognitive therapy individual	**39**	**-0.79 (-1.39 to -0.31)**
CT/CBT group	165	-0.26 (-1.12 to 0.60)	CBT group (under 15 sessions)	165	-0.26 (-0.68 to 0.16)
Problem solving individual	367	-0.86 (-1.75 to 0.01)	**Problem solving individual**	**367**	**-0.86 (-1.34 to -0.38)**
Counselling individual	404	-0.67 (-1.53 to 0.15)	**Non-directive/supportive/person-centred counselling**	**404**	**-0.67 (-1.05 to -0.30)**
IPT individual	146	-0.45 (-1.36 to 0.47)	IPT individual	146	-0.45 (-0.99 to 0.08)
Short-term PDPT individual	233	-0.58 (-1.35 to 0.10)	**Dynamic interpersonal therapy (DIT) individual**	**73**	**-0.71 (-1.58 to -0.02)**
			Short-term PDPT individual	**160**	**-0.46 (-0.90 to -0.01)**
SSRIs	**22,018**	**-0.24 (-0.32 to -0.16)**	**Citalopram**	**2,195**	**-0.22 (-0.31 to -0.12)**
			Escitalopram	**4,930**	**-0.27 (-0.37 to -0.19)**

			Fluoxetine	**6,031**	**-0.22 (-0.30 to -0.15)**
			Paroxetine	**5,861**	**-0.24 (-0.31 to -0.17)**
			Sertraline	**2,794**	**-0.24 (-0.32 to -0.16)**
TCAs	**4,524**	**-0.29 (-0.50 to -0.05)**	**Amitriptyline**	**2,462**	**-0.37 (-0.49 to -0.26)**
			Clomipramine	**345**	**-0.28 (-0.48 to -0.04)**
			Imipramine	**1,306**	**-0.29 (-0.42 to -0.15)**
			Lofepramine	**145**	**-0.33 (-0.60 to -0.10)**
			Nortriptyline	245	-0.17 (-0.40 to 0.15)
SNRIs	**9,538**	**-0.32 (-0.43 to -0.22)**	**Duloxetine**	**5,269**	**-0.33 (-0.42 to -0.25)**
			Venlafaxine	**4,269**	**-0.32 (-0.40 to -0.23)**
Mirtazapine	**1,884**	**-0.35 (-0.49 to -0.22)**	**Mirtazapine**	**1,884**	**-0.35 (-0.49 to -0.22)**
Trazodone	1,072	-0.13 (-0.29 to 0.04)	Trazodone	1,072	-0.13 (-0.29 to 0.04)
Acupuncture	264	-0.40 (-1.08 to 0.16)	Electroacupuncture	110	-0.41 (-0.91 to 0.04)
			Laser acupuncture	39	-0.57 (-1.60 to 0.12)
			Traditional acupuncture	115	-0.23 (-0.65 to 0.21)
Exercise individual	298	-0.13 (-1.24 to 1.10)	Supervised high intensity exercise individual	128	-0.16 (-0.68 to 0.37)
			Supervised low intensity exercise individual	117	-0.06 (-0.70 to 0.70)
			Unsupervised high intensity exercise individual	53	-0.19 (-0.64 to 0.26)
Exercise group	106	-0.19 (-1.20 to 0.87)	Supervised high intensity exercise group	69	-0.25 (-0.71 to 0.20)
			Supervised low intensity exercise group	37	-0.14 (-0.77 to 0.57)
Yoga group	65	-1.04 (-2.25 to 0.17)	Yoga group	65	-1.05 (-2.02 to -0.11)
CT/CBT individual + AD	**192**	**-1.18 (-2.07 to -0.44)**	**CBT individual (15 sessions or over) + any AD**	**10**	**-1.45 (-2.69 to -0.40)**
			CBT individual (15 sessions or over) + any SSRI	**43**	**-0.75 (-1.45 to -0.03)**
			CBT individual (15 sessions or over) + imipramine	25	-1.13 (-2.36 to 0.03)
			CBT individual (15 sessions or over) + nortriptyline	18	-1.00 (-2.16 to 0.13)
			CBT individual (under 15 sessions) + escitalopram	**48**	**-0.58 (-1.14 to -0.02)**
			CBT individual (under 15 sessions) + sertraline	**38**	**-1.37 (-2.94 to -0.07)**
			Third-wave cognitive therapy individual + any AD	**10**	**-2.07 (-3.35 to -0.84)**
CT/CBT group + AD	121	-1.23 (-2.95 to 0.41)	**CBT group (under 15 sessions) + any AD**	**63**	**-1.24 (-1.87 to -0.60)**

IPT individual + AD	99	-0.66 (-2.02 to 0.63)	**IPT individual + any AD**	**87**	**-0.63 (-1.26 to 0.00)**
			Interpersonal counselling individual + venlafaxine	12	-0.69 (-1.89 to 0.48)
Counselling individual + AD	57	0.21 (-2.52 to 2.96)	Non-directive/supportive/person-centred counselling + any AD	15	0.31 (-2.40 to 3.06)
			Non-directive/supportive/person-centred counselling + any SSRI	17	0.07 (-2.47 to 2.51)
			Non-directive/supportive/person-centred counselling + fluoxetine	25	0.17 (-3.01 to 3.18)
Short-term PDPT individual + AD	131	-0.34 (-2.36 to 1.64)	Short-term psychodynamic psychotherapy individual + any AD	113	-0.46 (-1.91 to 0.98)
			Short-term psychodynamic psychotherapy individual + any SSRI	18	-0.26 (-2.61 to 2.05)
Exercise group + AD	79	-1.37 (-2.75 to 0.01)	**Supervised high intensity exercise group + sertraline**	**42**	**-1.48 (-2.45 to -0.53)**
			Supervised low intensity exercise group + sertraline	**37**	**-1.25 (-2.26 to -0.23)**
Acupuncture + AD	**584**	**-0.78 (-1.12 to -0.44)**	**Electroacupuncture + any SSRI**	**160**	**-0.82 (-1.17 to -0.49)**
			Electroacupuncture + fluoxetine	**46**	**-0.74 (-1.15 to -0.26)**
			Electroacupuncture + paroxetine	**71**	**-0.85 (-1.22 to -0.53)**
			Traditional acupuncture + any SSRI	**206**	**-0.73 (-1.04 to -0.40)**
			Traditional acupuncture + paroxetine	**101**	**-0.77 (-1.09 to -0.45)**
Light therapy + AD	**54**	**-0.86 (-1.59 to -0.12)**	**Bright light therapy + fluoxetine**	**29**	**-0.92 (-1.51 to -0.36)**
			Bright light therapy + venlafaxine	**25**	**-0.80 (-1.41 to -0.16)**

Negative effect values indicate a favourable outcome for treatment classes and interventions compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.

AD: antidepressant; CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin uptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Sensitivity analyses

Effects on the SMD of all treatment classes versus TAU in the post-hoc sensitivity analysis that included only RCTs rated as being at low risk of bias for attrition in the Cochrane Risk of Bias tool are presented in Table 26, alongside the base-case analysis effects, to allow comparison between the two sets of results.

Table 26. Comparison of results following inclusion only of trials at low risk of bias for attrition in the NMA and results of the NMA base-case analysis: standardised mean difference (SMD) of depression symptom scores in adults with a new episode of more severe depression

Low risk of bias for attrition dataset			Full dataset – base-case analysis		
Treatment class	**N**	**Effect vs pill placebo (mean SMD, 95%CrI)**	**Treatment class**	**N**	**Effect vs pill placebo (mean SMD, 95%CrI)**
Problem solving group	28	**-2.92 (-5.87 to -0.03)**	Mindfulness or meditation group	15	**-3.69 (-5.16 to -2.23)**
Self-help without/with minimal support	198	**-2.13 (-4.43 to -0.25)**	Problem solving group	47	**-2.37 (-3.76 to -1.00)**
Exercise individual + AD	25	-1.65 (-3.74 to 0.34)	Yoga group + AD	15	**-1.91 (-3.64 to -0.24)**
CT/CBT individual + AD	131	**-1.62 (-3.06 to -0.33)**	Exercise group + AD	79	**-1.46 (-2.69 to -0.22)**
Peer support group + AD	42	-1.60 (-4.32 to 0.97)	Peer support group + AD	42	-1.49 (-3.10 to 0.04)
Peer support group	39	-1.48 (-4.34 to 1.38)	CT/CBT individual + AD	192	-1.25 (-1.97 to -0.62)
Exercise group + AD	79	-1.47 (-3.38 to 0.44)	Peer support group	39	-1.37 (-2.75 to 0.03)
CT/CBT group + AD	43	-1.28 (-3.96 to 1.29)	CT/CBT group + AD	63	-1.27 (-2.80 to 0.19)
Exercise individual	205	-1.17 (-2.61 to 0.30)	Exercise individual + AD	40	**-1.13 (-2.21 to -0.09)**
Light therapy + AD	54	-0.98 (-3.17 to 1.24)	Self-help without/with minimal support	344	-1.21 (-3.43 to 0.89)
Psychoeducation group	44	-0.95 (-3.78 to 1.88)	CT/CBT individual	1,044	**-1.00 (-1.71 to -0.38)**
Self-help with support	245	**-0.93 (-1.75 to -0.08)**	Behavioural therapies individual	378	**-1.01 (-1.98 to -0.08)**
Behavioural therapies individual	297	-0.91 (-3.80 to 1.91)	Psychoeducation group	44	-1.05 (-2.41 to 0.31)
Problem solving individual	367	-0.91 (-3.72 to 1.89)	Light therapy + AD	54	**-0.99 (-1.92 to -0.04)**
Short-term PDPT individual	99	-0.88 (-2.90 to 1.11)	Yoga group	65	-0.97 (-2.34 to 0.38)
IPT individual + AD	12	-0.86 (-3.58 to 1.87)	Acupuncture + AD	584	**-0.87 (-1.22 to -0.51)**
Acupuncture + AD	562	**-0.86 (-1.19 to -0.52)**	Relaxation individual + AD	10	-0.96 (-2.68 to 0.78)

CT/CBT individual	585	-0.83 (-2.50 to 0.76)	Short-term PDPT individual	233	-0.86 (-1.82 to 0.05)
Light therapy	32	-0.76 (-3.87 to 2.32)	IPT individual + AD	99	-0.81 (-1.96 to 0.29)
IPT individual	61	-0.74 (-3.56 to 2.06)	Behavioural therapies individual + AD	22	-0.85 (-2.51 to 0.83)
Counselling individual	315	-0.68 (-3.52 to 2.06)	Problem solving individual	367	-0.79 (-2.04 to 0.44)
Exercise group	55	-0.59 (-1.59 to 0.34)	Light therapy	32	-0.77 (-2.06 to 0.52)
TCAs	2,863	**-0.49 (-0.71 to -0.29)**	Self-help with support	267	-0.70 (-1.51 to 0.13)
Music therapy group	12	-0.46 (-3.39 to 2.45)	Music therapy group	12	-0.56 (-2.10 to 0.97)
Mirtazapine	1,465	**-0.43 (-0.57 to -0.30)**	Acupuncture	264	-0.56 (-1.42 to 0.23)
SNRIs	8,491	**-0.43 (-0.53 to -0.32)**	Counselling individual	404	-0.55 (-1.78 to 0.68)
SSRIs	18,032	**-0.32 (-0.39 to -0.25)**	Short-term PDPT + AD	131	-0.51 (-2.10 to 1.06)
CT/CBT group	145	-0.29 (-3.11 to 2.50)	IPT individual	146	-0.52 (-1.77 to 0.72)
Trazodone	972	**-0.20 (-0.37 to -0.04)**	Psychoeducation group + AD	27	-0.47 (-2.05 to 1.04)
Acupuncture	115	0.10 (-2.48 to 2.33)	CT/CBT group	165	-0.48 (-1.73 to 0.71)
			Mirtazapine	1,884	**-0.45 (-0.59 to -0.32)**
			TCAs	4,524	**-0.43 (-0.60 to -0.24)**
			Exercise group	106	-0.42 (-1.24 to 0.42)
			SNRIs	9,538	**-0.43 (-0.54 to -0.32)**
			Exercise individual	298	-0.32 (-1.59 to 1.01)
			Counselling individual + AD	57	-0.16 (-2.18 to 1.87)
			SSRIs	22,018	**-0.33 (-0.40 to -0.26)**
			Trazodone	1,072	-0.18 (-0.37 to 0.01)

Treatment classes ordered from best to worst, according to mean ranking in each analysis. Negative effect values indicate a favourable outcome for treatment classes compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
No RCTs at low risk of bias for attrition were identified for mindfulness or meditation group, problem solving individual, yoga, yog + AD, relaxation individual + AD, behavioural therapies individual + AD, short-term PDPT + AD, and counselling individual + AD; therefore these treatment classes were not included in the respective sensitivity analysis.
CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; TAU: treatment as usual

Finally, effects on the SMD of all treatment classes versus pill placebo in the sensitivity analysis conducted after excluding pharmacological trials are reported in Table 27, presented alongside the base-case analysis effects, to allow comparison between the two sets of results. In each analysis, treatment classes have been ordered from lowest to highest ranking (with lower rankings suggesting higher effects).

Table 27. Comparison of results following exclusion of pharmacological trials from the NMA and results of the NMA base-case analysis: standardised mean difference (SMD) of depression symptom change scores in adults with a new episode of more severe depression. TAU is used as the reference treatment, as the non-pharmacological dataset does not include pill placebo.

Non-pharmacological dataset			Full dataset – base-case analysis			
Treatment class	**N**	**Effect vs TAU (mean SMD, 95%CrI)**	**Treatment class**	**N**	**Effect vs pill placebo (mean SMD, 95%CrI)**	**Effect vs TAU (mean SMD, 95%CrI)**
Mindfulness or meditation group	15	**-3.66 (-5.55 to -1.79)**	Mindfulness or meditation group	15	**-3.69 (-5.16 to -2.23)**	**-3.47 (-4.95 to -1.99)**
Problem solving group	47	**-1.98 (-3.68 to -0.33)**	Problem solving group	47	**-2.37 (-3.76 to -1.00)**	**-2.15 (-3.55 to -0.76)**
Behavioural therapies individual	328	-1.21 (-2.61 to 0.19)	Self-help	344	-1.21 (-3.43 to 0.89)	-1.00 (-3.24 to 1.10)
Short-term PDPT individual	207	-1.15 (-2.60 to 0.27)	CT/CBT individual	1,044	**-1.00 (-1.71 to -0.38)**	**-0.78 (-1.52 to -0.12)**
Exercise individual	230	-1.25 (-3.27 to 0.75)	Behavioural therapies individual	378	**-1.01 (-1.98 to -0.08)**	-0.79 (-1.79 to 0.17)
CT/CBT individual	701	-1.03 (-2.18 to 0.06)	Psychoeducation group	44	-1.05 (-2.41 to 0.31)	-0.84 (-2.22 to 0.53)
Psychoeducation group	44	-1.03 (-2.82 to 0.76)	Yoga group	65	-0.97 (-2.34 to 0.38)	-0.76 (-2.13 to 0.62)
Yoga group	50	-0.94 (-2.89 to 0.99)	Short-term PDPT individual	233	-0.86 (-1.82 to 0.05)	-0.65 (-1.63 to 0.30)
Self-help without/with minimal support	344	-0.89 (-2.10 to 0.30)	Problem solving individual	367	-0.79 (-2.04 to 0.44)	-0.57 (-1.81 to 0.69)
CT/CBT group	42	-0.87 (-2.40 to 0.56)	Self-help with support	267	-0.70 (-1.51 to 0.13)	-0.50 (-1.35 to 0.33)
Problem solving individual	338	-0.74 (-2.18 to 0.68)	Music therapy group	12	-0.56 (-2.10 to 0.97)	-0.34 (-1.91 to 1.22)
Self-help with support	267	-0.69 (-1.96 to 0.57)	Counselling individual	404	-0.55 (-1.78 to 0.68)	-0.34 (-1.55 to 0.87)
Music therapy group	12	-0.53 (-2.44 to 1.40)	CT/CBT group	165	-0.48 (-1.73 to 0.71)	-0.27 (-1.51 to 0.93)
Exercise group	55	-0.52 (-1.69 to 0.65)	Exercise group	106	-0.42 (-1.24 to 0.42)	-0.21 (-1.04 to 0.66)
Counselling individual	404	-0.45 (-1.72 to 0.84)	Exercise individual	298	-0.32 (-1.59 to 1.01)	-0.10 (-1.38 to 1.24)

Treatment classes ordered from best to worst, according to mean ranking in each analysis. Negative effect values indicate a favourable outcome for treatment classes compared with pill placebo. Results where 95% CrI do not cross the no effect line are shown in bold.
CBT: cognitive behavioural therapy; CrI: credible intervals; CT: cognitive therapy; PDPT: psychodynamic psychotherapy; SMD: standardised mean difference; TAU: treatment as usual

Evidence from the pairwise meta-analyses

Important (but not critical) outcomes

See Table 28 for a summary of the clinically important and statistically significant effects observed for the important (but not critical) outcomes of quality of life and functioning (including personal, social, and occupational functioning and global functioning/functional impairment) at endpoint and longer-term (at least 6 months) follow-up. See supplement B3 for forest plots for all important (but not critical) outcomes.

Table 28. Summary of significant important (but not critical outcomes) at endpoint and longer-term (at least 6 months) follow-up for adults with a new episode of more severe depression

Intervention	Control	Outcome	Participants (N); Studies (K)	Effect estimate (95% CI)
CBT individual	No treatment	Functional impairment endpoint	N=137; K=1	SMD -0.78 [-1.13, -0.44]
CBT individual	Self-help with support	Quality of life endpoint	N=74; K=1	SMD 1.72 [1.13, 2.30]
CBT individual + SSRI	TAU	Quality of life endpoint	N=38; K=1	SMD -0.95 [-1.64, -0.27]
Problem solving individual	Attention placebo	Functional impairment endpoint	N=121; K=1	SMD -0.61 [-1.01, -0.21]
Problem solving individual	Non-directive counselling	Functional impairment endpoint	N=25; K=1	SMD -1.89 [-2.85, -0.92]
Non-directive counselling	No treatment	Functional impairment endpoint	N=258; K=1	SMD -1.60 [-1.88, -1.32]
IPT + SNRI	SNRI	Global functioning endpoint	N=31; K=1	SMD 0.92 [0.16, 1.68]
Self-help	No treatment	Quality of life endpoint	N=71; K=1	SMD 0.67 [0.18, 1.16]
Self-help	Waitlist	Functional impairment endpoint	N=183; K=1	SMD -0.74 [-1.04, -0.44]
Self-help with support	Waitlist	Sleeping difficulties endpoint	N=50; K=1	SMD -0.85 [-1.43, -0.27]
Short-term psychodynamic psychotherapy individual	CBT individual	Interpersonal problems endpoint	N=93; K=1	SMD -1.04 [-1.55, -0.52]
Short-term psychodynamic psychotherapy individual	Self-help with support	Quality of life endpoint	N=127; K=1	SMD 2.64 [2.16, 3.12]
Short-term psychodynamic psychotherapy individual	Self-help with support	Interpersonal problems endpoint	N=127; K=1	SMD -1.56 [-1.97, -1.16]
SSRI	Placebo	Sleeping difficulties change score	N=210; K=1	SMD -0.52 [-0.81, -0.23]
Exercise individual	No treatment	Quality of life endpoint	N=70; K=1	SMD 1.04 [0.54, 1.54]
Yoga group	Waitlist	Quality of life endpoint	N=43; K=1	SMD 2.01 [1.26, 2.76]

Abbreviations: CBT=cognitive behavioural therapy; SMD=standardised mean difference; SNRI= serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual

Follow-up of critical outcomes

See Table 29 for a summary of the clinically important and statistically significant effects observed for critical outcomes at longer-term (at least 6 months) follow-up. See supplement B3 for forest plots for all critical outcomes at all follow-up time points.

Table 29. Summary of significant critical outcomes at longer-term (at least 6 months) follow-up for adults with a new episode of more severe depression

Intervention	Control	Outcome	Participants (N); Studies (K)	Effect estimate (95% CI)
Behavioural individual	No treatment	Remission at 9-month follow-up	N=495; K=1	RR 1.33 [1.13, 1.57]
Behavioural individual	SSRI	Remission at 8-month follow-up	N=100; K=1	RR 2.42 [1.40, 4.18]
Behavioural individual	SSRI	Response at 8-month follow-up	N=100; K=1	RR 1.95 [1.35, 2.82]
CBT individual	TCA	Depression symptoms at 12-month follow-up	N=56; K=1	SMD -0.82 [-1.38, -0.27]
CBT individual + AD	AD	Depression symptoms at 6-12 month follow-up	N=79; K=2	SMD -0.63 [-1.08, -0.17]
Self-help	No treatment	Depression symptoms at 9-month follow-up	N=44; K=1	SMD -0.98 [-1.61, -0.36]
Self-help	No treatment	Remission at 9-month follow-up	N=62; K=1	RR 2.34 [1.05, 5.24]
Self-help	TAU	Depression symptoms at 6-month follow-up	N=68; K=1	SMD -0.61 [-1.11, -0.12]

Abbreviations: AD=antidepressant; CBT=cognitive behavioural therapy; RR=relative risk; SMD=standardised mean difference; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual; TCA=tricyclic antidepressant

Comparison of the results of pairwise meta-analysis with the NMA for critical outcomes

See Table 30 for comparisons between pairwise and NMA results for critical outcomes where the difference between the pairwise meta-analysis and NMA results is equal to, or larger than, the minimally important difference (default MID, defined as SMD -0.5/0.5 and logOR ±0.25 [MID for OR calculated as exp[0.25]=1.28]) and the effect estimate of the NMA is *not* within the 95% confidence interval of the pairwise effect estimate (considered a significant difference), and see Table 31 for differences between pairwise and NMA results ≥MID but where the NMA effect estimate is within the 95% confidence interval of the pairwise effect estimate (considered a non-significant difference). The full table of pairwise meta-analysis and NMA comparisons is available in supplement B4. Out of a total of 160 comparisons between pairwise and NMA results for more severe depression, 32 differences ≥MID were identified (20% of all comparisons), and of these only 17 differences (11% of all comparisons) could be considered significant in that the NMA estimate was not within the 95% confidence interval of the pairwise effect estimate. For most differences identified the difference was in magnitude rather than direction of effect and could probably be accounted for by the smaller evidence base contributing to the pairwise effect estimates. It is important to note that these comparisons have been performed in addition to the NMA inconsistency checks (where direct and indirect evidence is compared).

Table 30. Summary of differences between pairwise and NMA results ≥ MID where NMA effect estimate is not within 95% confidence interval of pairwise effect estimate for adults with a new episode of more severe depression

Intervention	Control	Outcome	Pairwise effect estimate (95% CI)	NMA effect estimate (95% CrI)
CBT individual	SNRI	Depression symptoms SMD	0.42 [-0.39, 1.23]	-0.55 [-1.28, 0.05]
CBT individual	SNRI	Response (ITT) OR	2.57 [0.60, 11.06]	0.37 [0.09, 1.05]
CBT individual	Pill placebo	Depression symptoms SMD	-0.47 [-0.84, -0.11]	-0.97 [-1.7, -0.38]
CBT group	No treatment	Depression symptoms SMD	-1.63 [-2.64, -0.61]	-0.55 [-1.8, 0.64]
Problem solving individual	Waitlist	Depression symptoms SMD	-0.86 [-1.11, -0.61]	-1.42 [-2.63, -0.17]
Non-directive counselling	No treatment	Depression symptoms SMD	-1.59 [-1.87, -1.31]	-0.63 [-1.83, 0.57]
Non-directive counselling	No treatment	Response (ITT) OR	5.22 [3.07, 8.86]	2.9 [0.32, 27.64]
Self-help	No treatment	Depression symptoms SMD	-0.20 [-0.80, 0.39]	-1.24 [-3.53, 0.79]
Self-help	Attention placebo	Depression symptoms SMD	-0.65 [-1.22, -0.09]	-1.37 [-3.75, 0.66]
Self-help with support	Self-help	Depression symptoms SMD	-0.20 [-1.01, 0.60]	0.47 [-1.78, 2.88]
Short-term psychodynamic psychotherapy individual	Self-help with support	Depression symptoms SMD	-0.65 [-1.01, -0.29]	-0.15 [-1.34, 1.04]
Short-term psychodynamic psychotherapy individual	Self-help with support	Remission (ITT) OR	10.07 [3.60, 28.16]	1.88 [0.25, 12.83]
Short-term psychodynamic psychotherapy individual	SSRI	Depression symptoms SMD	0.04 [-0.51, 0.58]	-0.52 [-1.48, 0.37]
Psychoeducation group	No treatment	Depression symptoms SMD	-1.68 [-2.19, -1.16]	-1.13 [-2.46, 0.19]
Mindfulness/ meditation group	No treatment	Depression symptoms SMD	-5.52 [-7.18, -3.86]	-3.76 [-5.19, -2.32]
Exercise individual + AD	No treatment	Depression symptoms SMD	-0.32 [-1.04, 0.40]	-1.19 [-2.29, -0.16]
Acupuncture	Waitlist	Response (ITT) OR	1.25 [0.47, 3.33]	4.52 [0.38, 63.25]

Abbreviations: AD=antidepressant; CBT=cognitive behavioural therapy; CI=confidence interval; ITT=intention-to-treat; NMA=network meta-analysis; OR=odds ratio; SMD=standardised mean difference; SNRI= serotonin and norepinephrine reuptake inhibitor; TAU=treatment as usual

Table 31. Summary of differences between pairwise and NMA results ≥ MID where NMA effect estimate is within 95% confidence interval of pairwise effect estimate for adults with a new episode of more severe depression

Intervention	Control	Outcome	Pairwise effect estimate (95% CI)	NMA effect estimate (95% CrI)
CBT individual	Waitlist	Depression symptoms SMD	-2.30 [-4.00, -0.61]	-1.61 [-2.36, -0.95]
CBT individual	Self-help	Depression symptoms SMD	-0.58 [-2.01, 0.85]	0.18 [-1.94, 2.5]
CBT individual	SNRI	Remission (ITT) OR	3.20 [0.72, 14.15]	0.97 [0.23, 4.22]

CBT group	Waitlist	Depression symptoms SMD	-2.89 [-6.27, 0.48]	-1.11 [-2.34, 0.1]
Problem solving individual	Non-directive counselling	Depression symptoms SMD	-0.73 [-1.41, -0.05]	-0.23 [-1.92, 1.46]
Problem solving group	Waitlist	Depression symptoms SMD	-3.53 [-4.28, -2.77]	-3 [-4.32, -1.67]
Problem solving group	Waitlist	Remission (ITT) OR	15.29 [4.12, 56.69]	18.89 [1.89, 215.7]
Self-help	Waitlist	Remission (ITT)	11.92 [6.63, 21.41]	9.85 [2.46, 44.2]
Self-help with support	Waitlist	Depression symptoms SMD	-1.84 [-2.48, -1.21]	-1.34 [-2.16, -0.53]
SSRI + exercise individual	Exercise individual	Depression symptoms SMD	-0.24 [-0.95, 0.48]	-0.8 [-2.45, 0.78]
Exercise group	TAU	Depression symptoms SMD	-0.74 [-1.32, -0.16]	-0.21 [-1.04, 0.66]
Yoga group	Waitlist	Depression symptoms SMD	-2.36 [-3.15, -1.56]	-1.61 [-2.93, -0.26]
Acupuncture	Waitlist	Remission (ITT) OR	2.13 [0.60, 7.58]	4.56 [0.65, 35.6]
Bright light therapy	SSRI	Remission (ITT) OR	3.24 [1.04, 10.05]	1.82 [0.22, 15.43]
Bright light therapy + SSRI	SSRI	Response (ITT) OR	7.68 [2.43, 24.29]	3.48 [0.22, 55.02]

Abbreviations: CBT=cognitive behavioural therapy; CI=confidence interval; ITT=intention-to-treat; NMA=network meta-analysis; OR=odds ratio; SMD=standardised mean difference; SNRI= serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TAU=treatment as usual

Pairwise meta-analysis of couple interventions

One RCT was included in pairwise meta-analysis of couple interventions for people with depression and problems in the relationship with their partner (Beach 1992).

The included study is summarised in Table 32.

Studies considered but not included in the pairwise meta-analysis of couple interventions are listed, and reasons for their exclusion are provided in appendix K.

Table 32. Summary of included study for couple interventions for adults with a new episode of more severe depression

Study	Population	Comparisons	Outcomes	Comments
Beach 1992 RCT US	N=45 Mean age (years): 39.1 Gender (% female): 100 Baseline severity: BDI mean 26.84 (SD=6.84)	Behavioural couples therapy versus waitlist Behavioural couples therapy versus CBT individual CBT individual versus waitlist	• Depression symptoms change score • Marital adjustment change score	• 3-arm trial • 15 weeks

CBT: cognitive behavioural therapy; SD: standard deviation

See the full evidence tables in appendix D, the forest plots in appendix E, and clinical evidence profiles in appendix F.

Subgroup analysis of studies included in the NMA

Subgroup analysis of studies included in the NMA was only possible for older adults (60 years and older) compared to younger adults (younger than 60 years), and not men or BME populations. Subgroup differences were examined for outcomes that had more than 2 studies in each subgroup.

Subgroup analysis was possible for 7 comparisons:

- SSRIs versus placebo:
    - 7 RCTs included for older adults (Bose 2008; Emsley 2018; Kasper 2005a; Nyth 1992; Rapaport 2009; Roose 2004; Tollefson 1993/1995 [1 RCT reported across 2 papers])
    - 99 RCTs included for younger adults (003-048; 29060 07 001; Andreoli 2002/Dubini 1997/Massana 1998_study 1 [1 RCT reported across 3 papers]; Baune 2018; Binnemann 2008; Bjerkenstedt 2005; Blumenthal 2007/Hoffman 2011 [1 RCT reported across 2 papers]; Burke 2002; Byerley 1988; CAGO178A2303; CL3-20098-022; CL3-20098-023; CL3-20098-024; Claghorn 1992a; Claghorn 1992b; Clayton 2006_study 1; Clayton 2006_study 2; Coleman 2001; Corrigan 2000; Detke 2004; Doogan 1994; Dube 2010; Dunbar 1993; Eli Lilly HMAT-A; Fabre 1992; Fabre 1995a; Fava 1998a; Fava 2005; Feighner 1993; Feighner 1999; Forest Laboratories 2000; Forest Laboratories 2010; Forest Research Institute 2003; Forest Research Institute 2005; Godlewska 2012; Golden 2002_448; Golden 2002_449; Goldstein 2002; Goldstein 2004; Griebel 2012_Study DFI5878; Griebel 2012_Study DFI5879; Gual 2003; Higuchi 2009; Higuchi 2011; Hirayasu 2011a; Hirayasu 2011b; Hunter 2010_study 1; Hunter 2011; Jefferson 2000; Kasper 2012; Katz 2004; Keller 2006_Study 059; Keller 2006_Study 061; Keller 2006_Study 062; Komulainen 2018; Kramer 1998; Kranzler 2006_Group A; Lam 2016; Lepola 2003; Loo 2002; Lopez-Rodriguez 2004; M/2020/0046 (Study 046); M/2020/0046 (Study 047); Macias-Cortes 2015; Mathews 2015; Mendels 1999; Miller 1989a; Mundt 2012; MY-1042/BRL-029060/CPMS-251; MY-1045/BRL-029060/1 (PAR 128); NCT01020799; Nemeroff 2007; Nierenberg 2007; NKD20006 (NCT00048204); Olie 1997; PAR 01 001 (GSK & FDA); PAR 279 MDUK; Perahia 2006; Peselow 1989a; Peselow 1989b; Ratti 2011_study 096; Ravindran 1995; Reimherr 1990; Rickels 1992; Rudolph 1999; SER 315 (FDA); Sheehan 2009b; Smith 1992; Sramek 1995; Stark 1985; Study 62b (FDA); Study F1J-MC-HMAQ - Study Group B; Trivedi 2004; Valle-Cabrera 2018; Wade 2002; Wang 2014c; WELL AK1A4006; Wernicke 1987; Wernicke 1988)
- SSRIs versus TCAs:
    - 12 RCTs included for older adults (Cohn 1990b; De Ronchi 1998; Forlenza 2001; Geretsegger 1995; GSK_29060/103; Guillibert 1989; Hutchinson 1992; Kyle 1998; MDF/29060/III/070/88/MC; Mulsant 1999; Navarro 2001; Sneed 2014)
    - 55 RCTs included for younger adults (29060/299; 29060 07 001; Akhondzadeh 2003; Bascara 1989; Beasley 1993b; Bersani 1994; Bhargava 2012; Bremner 1984; Byerley 1988; Chiu 1996; Christiansen 1996; Cohn 1984b; Danish University Antidepressant Group 1986; Danish University Antidepressant Group 1990; Demyttenaere 1998; Deushle 2003; Fabre 1991; Fabre 1992; Fawcett 1989; Feighner 1993; Freed 1999; Hashemi 2012; Judd 1993; Keegan 1991; Laakmann 1991; Levine 1989; Marchesi 1998; Miura 2000; Moller 1993; Moller 1998; Moller 2000; Moon 1994; Moon 1996; Nielsen 1993; Noguera 1991; Ontiveros Sanchez 1998; PAR 29060/281; PAR MDUK 032; Peselow 1989a; Peselow 1989b; Peters 1990; Preskorn 1991; Reimherr 1990; Ropert 1989; Rosenberg 1994; SER 315 (FDA); SER-CHN-1; Serrano-

Blanco 2006; Shaw 1986; Staner 1995; Stark 1985; Suleman 1997; Tollefson 1994; Versiani 1999; Young 1987)

- TCAs versus placebo
  - 6 RCTs included for older adults (Cohn 1984a; Georgotas 1986; Katz 1990; Nair 1995; Reynolds 1999a; Schweizer 1998)
  - 50 RCTs included for younger adults (29060 07 001; Amsterdam 1986; Barge-Schaapveld 2002; Bakish 1992b; Blashki 1971; Bremner 1995; Byerley 1988; Cassano 1986; Elkin 1989/Imber 1990 [1 RCT reported across 2 papers]; Escobar 1980; Fabre 1992; Feiger 1996; Feighner 1979; Feighner 1982; Feighner 1989b; Feighner 1993; Fontaine 1994; Gelenberg 1990a; Goldberg 1980; Hicks 1988; Kleber 1983; Kusalic 1993; Lecrubier 1997; March 1990; McCallum 1975; MIR 003-020 (FDA); MIR 003-021 (FDA); Mynors-Wallis 1995; Norton 1984; Peselow 1989a; Peselow 1989b; Philipp 1999; Reimherr 1990; Rickels 1982b; Rickels 1982d; Rickels 1982e; Rickels 1987; Rickels 1991; Rickels 1994; Rickels 1995_Study 006-1; Rickels 1995_Study 006-2; Schweizer 1994; SER 315 (FDA); Silverstone 1994; Smith 1990; Stark 1985; Stassen 1993; Thomson 1982; Versiani 1989; White 1984)
- SNRIs versus placebo
  - 3 RCTs included for older adults (Katona 2012; Raskin 2007; Robinson 2014)
  - 36 RCTs included for younger adults (Baldwin 2012; Boulenger 2014; Brannan 2005; Cunningham 1994; Cunningham 1997; Cutler 2009; Detke 2002a; Detke 2002b; Detke 2004; Eli Lilly HMAT-A; Goldstein 2002; Goldstein 2004; Guelfi 1995; Hewett 2009; Hewett 2010; Higuchi 2009; Higuchi 2016; Hunter 2010_study 2; Hunter 2010_study 3; Khan 1991; Lecrubier 1997; Levin 2013; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mendels 1993; Nemeroff 2007; Nierenberg 2007; Perahia 2006; Rudolph 1999; Schweizer 1991; Schweizer 1994; Sheehan 2009b; Study F1J-MC-HMAQ - Study Group B; Thase 1997; VEN 600A-303 (FDA); VEN 600A-313 (FDA))
- SNRIs versus TCAs
  - 2 RCTs included for older adults (Gasto 2003; Smeraldi 1998b)
  - 6 RCTs included for younger adults (Benkert 1996; Dubey 2012; Gentil 2000; Lecrubier 1997; Samuelian 1998; Schweizer 1994)
- SNRIs versus SSRIs
  - 3 RCTs included for older adults (Allard 2004; Hwang 2004; Schatzberg 2000)
  - 36 RCTs included for younger adults (Alves 1999; Basterzi 2009; Bielski 2004; Casabona 2004; Clerc 1994; Costa 1998; DeNayer 2002; Detke 2004; Diaz-Martinez 1998; Dierick 1996; Eli Lilly HMAT-A; Goldstein 2002; Goldstein 2004; Hao 2014; Heller 2009; Higuchi 2009; Jiang 2017; Khan 2007; Kornaat 2000; Lee 2007; Mehtonen 2000; Montgomery 2004; Mowla 2016; Nemeroff 2007; Nierenberg 2007; Owens 2008; Perahia 2006; Rickels 2000; Rudolph 1999; Sheehan 2009b; Shelton 2006; Sir 2005; Study F1J-MC-HMAQ - Study Group B; Tylee 1997; Tzanakaki 2000; Wade 2007)
- Trazodone versus TCAs
  - 3 RCTs included for older adults (Altamura 1989a; Ather 1985; Smeraldi 1998b)
  - 3 RCTs included for younger adults (Escobar 1980; Goldberg 1980; Moises 1981)

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison SSRIs versus placebo shows non-significant subgroup differences for: depression symptoms endpoint (Test for subgroup differences: $Chi^2 = 1.53$, df = 1, p = 0.22); depression symptoms change score (Test for subgroup differences: $Chi^2 = 1.62$, df = 1, p = 0.20); remission (Test for subgroup differences: $Chi^2 = 1.38$, df = 1, p = 0.24); response (Test for subgroup differences: $Chi^2 = 0.24$, df = 1, p = 0.63); discontinuation due to side effects (Test for subgroup differences: $Chi^2 = 0.02$, df = 1, p = 0.88);

discontinuation due to any reason (Test for subgroup differences: Chi² = 2.62, df = 1, p = 0.11).

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison SSRIs versus TCAs shows non-significant subgroup differences for: depression symptoms endpoint (Test for subgroup differences: Chi² = 0.20, df = 1, p = 0.65); depression symptoms change score (Test for subgroup differences: Chi² = 0.11, df = 1, p = 0.75); remission (Test for subgroup differences: Chi² = 1.60, df = 1, p = 0.21); response (Test for subgroup differences: Chi² = 1.67, df = 1, p = 0.20); discontinuation due to side effects (Test for subgroup differences: Chi² = 1.85, df = 1, p = 0.17); discontinuation due to any reason (Test for subgroup differences: Chi² = 0.79, df = 1, p = 0.37).

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison TCAs versus placebo shows non-significant subgroup differences for: remission (Test for subgroup differences: Chi² = 0.41, df = 1, p = 0.52); response (Test for subgroup differences: Chi² = 0.88, df = 1, p = 0.35); discontinuation due to side effects (Test for subgroup differences: Chi² = 0.05, df = 1, p = 0.83); discontinuation due to any reason (Test for subgroup differences: Chi² = 0.02, df = 1, p = 0.88). Subgroup analysis was not possible for the outcomes depression symptoms endpoint, and depression symptoms change score, as there were not at least 2 studies per subgroup for these outcomes.

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison SNRIs versus placebo shows non-significant subgroup differences for: depression symptoms change score (Test for subgroup differences: Chi² = 0.07, df = 1, p = 0.79); remission (Test for subgroup differences: Chi² = 0.01, df = 1, p = 0.91); response (Test for subgroup differences: Chi² = 0.04, df = 1, p = 0.85); discontinuation due to side effects (Test for subgroup differences: Chi² = 0.93, df = 1, p = 0.34); discontinuation due to any reason (Test for subgroup differences: Chi² = 0.59, df = 1, p = 0.44). Subgroup analysis was not possible for depression symptoms endpoint as there were not at least 2 studies per subgroup for this outcome.

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison SNRIs versus TCAs shows non-significant subgroup differences for: discontinuation due to side effects (Test for subgroup differences: Chi² = 0.10, df = 1, p = 0.75); discontinuation due to any reason (Test for subgroup differences: Chi² = 1.33, df = 1, p = 0.25). Subgroup analysis was not possible for the outcomes depression symptoms endpoint, depression symptoms change score, remission, and response, as there were not at least 2 studies per subgroup for these outcomes.

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison SNRIs versus SSRIs shows non-significant subgroup differences for: remission (Test for subgroup differences: Chi² = 0.01, df = 1, p = 0.94); response (Test for subgroup differences: Chi² = 0.87, df = 1, p = 0.35); discontinuation due to side effects (Test for subgroup differences: Chi² = 0.03, df = 1, p = 0.85); discontinuation due to any reason (Test for subgroup differences: Chi² = 0.00, df = 1, p = 0.97). Subgroup analysis was not possible for the outcomes depression symptoms endpoint, and depression symptoms change score, as there were not at least 2 studies per subgroup for these outcomes.

Subgroup analysis of older adults (60 years and older) compared to younger adults (younger than 60 years) for the comparison trazodone versus TCAs shows non-significant subgroup differences for: discontinuation due to side effects (Test for subgroup differences: Chi² = 0.01, df = 1, p = 0.92); discontinuation due to any reason (Test for subgroup differences: Chi² = 0.89, df = 1, p = 0.35). Subgroup analysis was not possible for the outcomes depression symptoms endpoint, depression symptoms change score, remission, and response, as there were not at least 2 studies per subgroup for these outcomes.

Quality assessment of studies included in the evidence review and the evidence

A threshold analysis was originally planned to conduct, to test the robustness of treatment recommendations based on the NMA, to potential biases or sampling variation in the included evidence. Threshold analysis has been developed as an alternative to GRADE for assessing confidence in guideline recommendations based on network meta-analysis (Phillippo 2019). Threshold analysis suggests by how much effects that have been estimated in the NMA need to change before recommendations change, and whether such changes might potentially occur due to bias in the evidence. The NICE Guidelines Technical Support Unit (TSU) attended committee discussions on the rationale for recommendations and noted that, in addition to the results of the NMA, the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The TSU advised that as it was difficult to identify a clear decision rule to link the recommendations directly to the NMA results, it was not feasible or helpful to conduct a threshold analysis. CINeMA was also considered as a method to evaluate the confidence in the results from the NMA (Nikolakopoulou 2020). However, this was not possible to carry out, due to the class models being implemented.

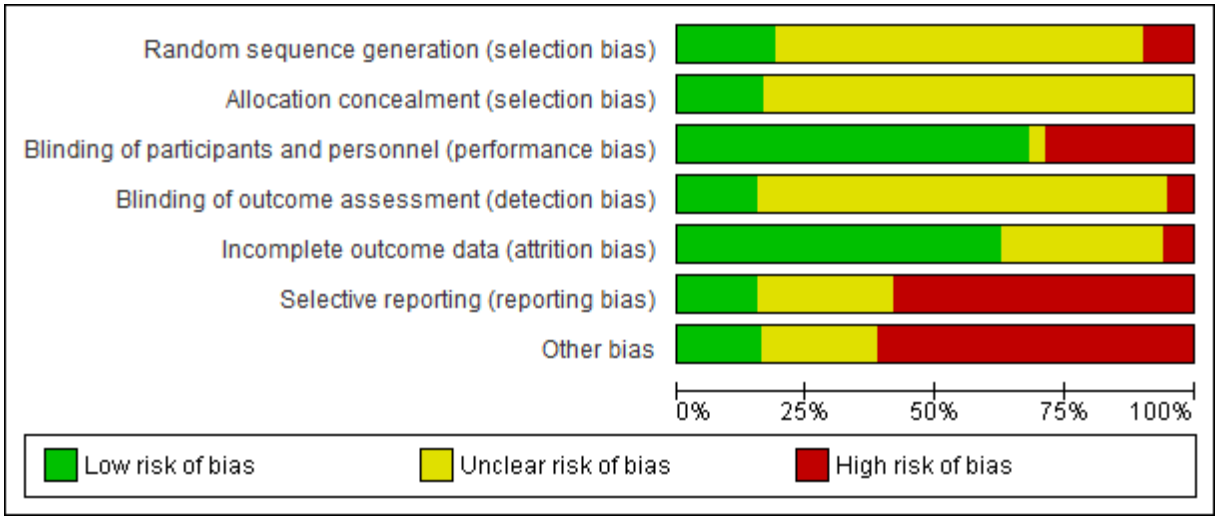
In the absence of undertaking threshold analysis or using CINeMA to evaluate the quality of the evidence and the confidence in the results derived from the NMA that informed this review question, we evaluated and summarise the quality of the evidence narratively, using the domains considered as per a standard GRADE approach (risk of bias, inconsistency, publication bias, indirectness and imprecision).

For outcomes analysed only in pairwise meta-analysis (couple interventions), see the clinical evidence profiles in appendix F.

Risk of bias

The Cochrane risk of bias tool version 1.0 for RCTs (see appendix H in Developing NICE guidelines: the manual; NICE 2014) was used to assess potential bias in each study included in the review. Generally the standard of reporting in studies was quite low, as demonstrated by the risk of bias summary diagram (Figure 16). Of the studies included in the NMAs for more severe depression, 106 were at low risk for allocation method, and 86 were at low risk of bias for allocation concealment. Trials of psychological therapies were typically considered at high risk of bias for participant and provider blinding, although it is difficult to quantify in risk of bias ratings it is also important to bear in mind that the rate of side effects may also make it difficult to maintain blinding in pharmacological trials. Across interventions, 364 trials were at low risk of bias for blinding participants and providers. Most reported outcomes were investigator-rated, and assessor blinding was considered for all trials: 82 were at low risk of bias, 423 were unclear, and high risk in 29 trials. For attrition bias, 330 trials were at low risk of bias, unclear risk in 173 trials, and 31 trials were at high risk of bias. For selective reporting bias, 77 trials were at low risk of bias, unclear risk in 143 trials, and 314 trials were at high risk of bias. Other sources of bias, predominantly potential conflict of interest based on the source of funding, were identified in 455 RCTs. See appendix D for full study details, including risk of bias ratings by study.

Figure 16. Risk of bias summary for treatments of a new episode in people with more severe depression



Model goodness of fit and inconsistency

This section reports only findings of goodness of fit and inconsistency checks for the NMAs that informed the clinical evidence. Respective findings for the NMAs that informed the economic analysis are reported in appendix J. Detailed findings of goodness of fit and inconsistency checks for all NMA analyses, including those that informed the guideline economic model, are reported in appendix M and supplements B5 and B6.

For the SMD of depressive symptom scores, relative to the size of the treatment effect estimates, moderate between trial heterogeneity was observed for this outcome, as expressed by the between-studies standard deviation [τ=0.19 (95% CrI 0.15 to 0.23)]. Between-study heterogeneity and posterior mean residual deviance were slightly lower in the inconsistency model than in the random effects consistency model. The inconsistency model notably predicted the data in three studies much better than the consistency model, further adding evidence of inconsistency.

For the outcome of response in those randomised, moderate between trials heterogeneity was found relative to the size of the intervention effect estimates [τ=0.26 (95% CrI 0.21 to 0.31)]. Lower posterior mean residual deviance and between study heterogeneity in the inconsistency model suggested evidence of inconsistency. The inconsistency model notably predicted the data in one study (Sahranavard 2018) much better than the consistency model, further adding evidence of inconsistency. This study compared waitlist, dialectical behavioural therapy (DBT) individual and CBT group (under 15 sessions).

For the outcome of remission in those randomised, moderate between trials heterogeneity was found relative to the size of the intervention effect estimates [τ=0.27 (95% CrI 0.20 to 0.34)]. No meaningful differences were observed in posterior mean residual deviance, though DIC was slightly lower in the random effects consistency model, and between-study heterogeneity slightly lower in the inconsistency model. The prediction of several individual studies was worse in the consistency model, suggesting some evidence of inconsistency. These studies investigated behavioural activation individual, CBT individual (15 sessions or over), sertraline, impiramine and venafalxine.

Detailed model fit statistics, heterogeneity and results of inconsistency checks for each outcome are provided in appendix M and supplements B5 and B6. Comparisons between the relative effects of all pairs of treatments obtained from the consistency (NMA) model and those obtained from the inconsistency (pairwise) model are also provided in supplement B6 for all outcomes considered in the NMA.

Selective outcome reporting and publication bias

Bias adjustment models on the SMD of depressive symptom scores were developed to assess potential bias associated with small study size. The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model suggesting strong evidence of small study bias in comparisons between active and inactive interventions in the SMD outcome, in adults with more severe depression.

The bias adjusted model resulted in small to moderate changes in the relative effects of all treatment classes versus pill placebo (reference treatment) and had also a moderate impact on some class rankings. Results are presented in the previous section of this evidence review.

Detailed results of all bias models are provided in appendix M and supplements B5 and B6.

Indirectness

In the context of the NMA, indirectness refers to potential differences across the populations, interventions and outcomes of interest, and those included in the relevant studies that informed the NMA.

A key assumption when conducting NMA is that the populations included in all RCTs considered in the NMA are similar. However, participants in pharmacological and non-pharmacological (psychological or physical intervention) trials may differ to the extent that some participants find different interventions more or less acceptable in light of their personal circumstances and preferences (so that they might be willing to participate in a pharmacological trial but not a psychological one and vice versa). Similarly, self-help trials may recruit participants who would not seek or accept face-to-face interventions. However, a number of trials included in the NMA have successfully recruited participants who are willing to be randomised to either pharmacological or psychological intervention and to either self-help or face-to-face treatment. The NMAs have assumed that service users are willing to accept any of the interventions included in the analyses; in practice, treatment decisions may be influenced by individual values and goals, and people's preferences for different types of interventions. These factors were taken into account when formulating recommendations.

In addition, to explore the transitivity assumption in the context of participants in pharmacological and non-pharmacological trials, a sensitivity analysis on the SMD outcome was conducted after excluding trials with at least one pharmacological or combined intervention arm, where the combined intervention included a pharmacological element. The purpose was to compare the relative effects and rankings of non-psychological treatments between this sensitivity analysis and the base-case analysis. The comparison, which is presented in Table 27, suggested some changes in effects and rankings after exclusion of pharmacological trials, and higher uncertainty in the effects, apparently because the majority of the evidence came from pharmacological trials in this dataset (treatments for a new episode of more severe depression).

A post-hoc sensitivity analysis that included only RCTs rated as being at low risk of bias was conducted on the SMD outcome, which was the primary critical outcome of the clinical analysis. Such analysis was only possible to conduct for the domain of 'attrition' in the risk of bias tool, as this was the only domain that included a sufficient number of RCTs at low risk of bias, and a relatively wide range of treatment classes.This sub-group analysis showed no substantial difference in treatment effects compared with the base-case analysis, suggesting that bias from attrition was unlikely to be an effect modifier in this population.

Interventions of similar type were grouped in classes following the committee's advice and considered in class models. These models allowed interventions within each class to have

similar, but not identical, effects around a class mean effect. Classes and interventions assessed in the NMAs were directly relevant to the classes and interventions of interest.

Outcomes reported in included studies were also the primary outcomes of interest, as agreed by the committee.

Imprecision

There were wide 95%CrI around mean effects and rankings, for most treatment classes versus the reference treatment (pill placebo) across all NMA outcomes. For several treatment classes, the 95%CrI around relative effects versus pill placebo crossed the line of no effect.

Overall rating of the quality of the evidence

Based on the narrative assessment of the quality of the evidence using the domains considered as per a standard GRADE approach, the quality of the evidence was considered to be low-to-moderate.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline. See the literature search strategy in appendix B and economic study selection flow chart in appendix G. Details on the hierarchy of inclusion criteria for economic studies are provided in supplement 1 - Methods. For this review question, only economic studies conducted in the UK were included.

The systematic search of the economic literature identified 11 studies that assessed the cost effectiveness of interventions for adults with a new episode of more severe depression in the UK (Miller 2003, Romeo 2004, Wade 2005a, Wade 2005b, Simon 2006, Wade 200, Lenox-Smith 2009, Benedict 2010, Gilbody 2015/Littlewood 2015, Koeser 2015, Hollingworth 2020). Categorisation of the studies according to their population's severity level of depressive symptoms followed the same criteria used for the categorisation of the clinical studies included in the guideline systematic review. Where study participants' baseline scores on a depressive symptom scale were not provided, categorisation was based on the description of the participants' depressive symptom severity in the study.

Economic evidence tables are provided in appendix H. Economic evidence profiles are shown in appendix I.

Excluded studies

A list of excluded economic and utility studies, with reasons for exclusion, is provided in supplement 3 - Economic evidence included & excluded studies.

Summary of studies included in the economic evidence review

All included economic studies were conducted in the UK and adopted a NHS perspective, with some studies including personal social service (PSS) costs as well; in addition, some studies reported separate analyses that adopted a societal perspective. NHS and PSS cost elements included, in the vast majority of studies, intervention, primary and community care, staff time (such as GPs, nurses, psychiatrists, psychologists), medication, inpatient and outpatient care and other hospital care. All studies used national unit costs; in some studies, intervention costs were based on local prices or prices provided by the manufacturers (for example, in the case of computerised CBT packages).

Self-help with support: computerised cognitive behavioural therapy with support

Gilbody 2015/Littlewood 2015 conducted an economic analysis alongside a RCT (Gilbody 2015/Littlewood 2015, N=691; at 24 months EQ-5D data available for n=416 and NHS cost data available for n=580) to assess the cost effectiveness of 2 computerised CBT programmes with therapist support (the commercially produced package Beating the Blues and the free to use package MoodGYM) versus treatment as usual in adults with depression in the UK. The outcome measure was the QALY estimated based on EQ-5D ratings (UK tariff). The duration of the analysis was 2 years.

Using a NHS and PSS perspective, the commercially produced computerised CBT was more expensive than treatment as usual, and the freely available computerised CBT was less costly than treatment as usual. Treatment as usual produced a higher number of QALYs than either of the 2 computerised CBT packages. Thus, the commercially produced computerised CBT was dominated by treatment as usual. The ICER of treatment as usual versus the free-to-use computerised CBT package was £7,798 per QALY (2020 prices). The probability of treatment as usual being cost-effective across the 3 treatment options was 0.55 at the lower NICE cost effectiveness threshold of £20,000 per QALY. Using QALYs generated based on the SF-6D, the commercially produced computerised CBT programme was still dominated by treatment as usual; in contrast, the freely available computerised CBT programme became the dominant option; under this scenario, the probability of the freely available computerised CBT programme being cost effective at the lower NICE cost effectiveness threshold became 0.76. Results were robust to inclusion of depression-related costs only and to consideration of completers' data only (instead of imputed data analysis). Moreover, there was little evidence of an interaction effect between preference and treatment allocation on outcomes. These results suggest that computerised CBT with support is unlikely to be cost-effective within the NICE decision-making context (which recommends use of EQ-5D for generation of QALYs). The study is directly applicable to the UK context and is characterised by minor limitations.

Non-directive counselling versus antidepressants

Miller and colleagues (2003) compared the cost effectiveness of non-directive counselling (generic psychological therapy comprising 6 weekly 50-minute sessions) versus routinely prescribed antidepressant drugs (mainly dothiepin, fluoxetine or lofepramine) in adults with moderate to severe depression in the UK. The study was conducted alongside a RCT (Bedi 2000; N=103, at 12 months efficacy data for n=81 and resource data for n=103). People refusing randomisation but agreeing to participate in the patient preference trial were given the treatment of their choice (N=220; at 12 months efficacy data for n=163 and resource use data n=215). The study included only depression-related costs. The measure of outcome was a 'global outcome', assessed by a psychiatrist blind to treatment allocation, using the research diagnostic criteria (RDC), the patient's BDI score and GP notes. The outcome was considered good if the person responded to treatment within 8 weeks and then remained well. The outcome measure of the analysis was 12 months.

In the RCT, antidepressants were more costly and more effective than non-directive counselling, with an ICER of £524 per extra person with a good global outcome (2020 prices). The probability of non-directive counselling being cost-effective was 0.25 and 0.10 at a cost effectiveness threshold of £995 and £3,983 per extra person with a good global outcome, respectively. Sensitivity analysis demonstrated that, assuming missing data reflected good outcomes, the probability of counselling being cost-effective increased at any cost effectiveness threshold; assuming that missing data represented poor outcomes, the probability of non-directive counselling being cost-effective slightly increased for cost effectiveness thresholds lower than £2,987 per good global outcome and decreased for cost effectiveness thresholds higher than £2,987 per good global outcome. In the preference trial, non-directive counselling was more costly and more effective than antidepressants with an ICER of £1,816 per extra person with a good global outcome. The study is partially

applicable to the NICE decision-making context as it does not use the QALY as the measure of benefit and is characterised by potentially serious limitations, such as the inclusion of depression-related costs only, the use of local unit costs for counsellors, the small numbers of participants randomised as well as included in the preference trial, and the contradictory results between the RCT and the preference trial which did not allow robust conclusions to be drawn.

Antidepressants (various comparisons between SSRIs, SNRIs, TCAs, mirtazapine)

Sertraline versus placebo

Hollingworth 2020 evaluated the cost effectiveness of sertraline versus placebo in adults presenting to primary care with depression or low mood during the past 2 years. The economic analysis was conducted alongside a RCT (Lewis 2019, N=655; EQ-5D data available for n=505; cost data available for n=381). The measure of outcome was the QALY, estimated based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 12 weeks.

Under a NHS and personal social services perspective, sertraline was found to dominate placebo, as it was both more effective and less costly. Its probability of being cost-effective at the NICE lower cost effectiveness threshold of £20,000/QALY was over 95%. Subgroup analysis showed that sertraline was cost-effective in the treatment of mild, moderate and severe depression. The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Escitalopram versus citalopram and venlafaxine

Wade 2005a and 2005b undertook model-based economic analysis to assess the cost effectiveness of escitalopram compared with citalopram and venlafaxine in adults with major depression (Wade 2005a) and escitalopram compared with citalopram in the subgroup of adults with severe major depression (Wade 2005b). The analyses utilised pooled efficacy data from published RCTs. Resource use data were based on information from a general practice research database, published literature and expert opinion. The measure of outcome was the percentage of people with remission in each arm of the model, defined as a MADRS score ≤ 12. The time horizon of the analyses was 26 weeks.

In both models, under a NHS perspective, escitalopram dominated both citalopram and venlafaxine (it was more effective and less costly). Results were robust to changes in clinical and cost model parameters. In adults with severe depression, escitalopram was dominant in more than 99.8% of the probabilistic analysis iterations. The studies are directly applicable to the NICE decision-making context, as, although the QALY was not used as an outcome, results were straightforward to interpret. However, both studies are characterised by potentially serious limitations, such as the lack of consideration of side effects and their impact on costs and outcomes (Wade 2005a), the estimation of resource use based primarily on expert opinion, and the presence of conflicts of interest as both studies were funded by industry.

Escitalopram versus duloxetine

Wade 2008 evaluated the cost effectiveness of escitalopram versus duloxetine in adults with moderate-to-severe depression. The economic analysis was conducted alongside an international RCT (Wade 2007, N=295; health economic data available for n=223). The measures of outcome were the change in Sheehan Disability Scale score, the change in the Montgomery-Asperg Depression Rating Scale (MADRS) score; response and remission. The time horizon of the analysis was 24 weeks.

Under a NHS perspective, escitalopram was found to dominate duloxetine, as it was both more effective and less costly. The study is directly applicable to the NICE decision-making

context because although it did not use the QALY as an outcome, the intervention was dominant. The analysis is characterised by potentially serious limitations, mainly lack of probabilistic sensitivity analysis and presentation of cost-effectiveness acceptability curves, and the presence of conflicts of interest as both studies were funded by industry.

Paroxetine versus mirtazapine

Romeo 2004 evaluated the cost effectiveness of paroxetine versus mirtazapine in adults with moderate-to-severe depression. The economic analysis was conducted alongside a RCT (Wade 2003, N=197; data used in economic analysis n=177). The measures of outcome were the % of response defined as at least 50% decrease in HAMD17 and changes in Quality of Life in Depression Scale (QLDS) from baseline to treatment endpoint. The time horizon of the analysis was 24 weeks.

Under a NHS and social care perspective, mirtazapine was found to dominate paroxetine, as it was both more effective and less costly. The study is directly applicable to the NICE decision-making context because although it did not use the QALY as an outcome, the intervention was dominant. The analysis is characterised by potentially serious limitations, mainly that is was based on a relatively small RCT and that results are subject to bias as the study was funded by industry.

Duloxetine versus SSRIs, venlafaxine and mirtazapine

Benedict 2010 constructed an economic model to evaluate the cost effectiveness of SSRIs, duloxetine, venlafaxine and mirtazapine in adults with moderate to severe major depression that had a new treatment episode and were treated in primary care in the UK. Efficacy data were obtained from meta-analyses of RCTs, with randomisation rules possibly being broken. Resource use estimates were based on expert opinion. The outcome measure was the QALY, based on EQ-5D ratings (UK tariff). The duration of the analysis was 48 weeks.

Under the Scottish NHS perspective, duloxetine was the most cost-effective intervention as it dominated venlafaxine and had an ICER versus SSRIs of £9,700/QALY (2020 prices). SSRIs dominated mirtazapine. The probability of duloxetine being cost-effective at the NICE lower cost-effectiveness threshold of £20,000/QALY was approximately 70%. Results were sensitive to the efficacy and utility data used. Although the study is directly applicable to the NICE decision-making context, it is characterised by potentially serious limitations, including the methods for meta-analysis and evidence synthesis (selective use of RCTs and synthesis that appears to have potentially broken randomisation) and the fact that it was funded by industry, which may have introduced bias in the analysis.

Fluoxetine versus amitriptyline versus venlafaxine

Lenox-Smith 2009 updated an economic model developed by the same research team to assess the cost effectiveness of fluoxetine versus amitriptyline and venlafaxine in people with more severe depression in the UK. Efficacy data were taken from synthesis of a meta-analysis of trials (fluoxetine versus venlafaxine) and a single trial (amitriptyline versus venlafaxine). The method of synthesis was unclear, but most likely randomisation was broken. Resource use data were elicited from a Delphi panel. The measure of outcome was the QALY, estimated based on the presumed utilities of a depression-free day and a severely depressed day. The time horizon of the analysis was 24 weeks. Venlafaxine was found to dominate both fluoxetine and amitriptyline, with results being robust to changes in costs but sensitive to the value of the utility gain associated with a depression-free day. The study is partially applicable to the NICE decision-making context (the method of QALY estimation is not consistent with NICE recommendations) and, more importantly, is characterised by very serious limitations, mainly concerning the method of evidence synthesis.

Combined CBT with antidepressant (fluoxetine) versus antidepressant alone

Simon 2006 developed an economic model to assess the cost effectiveness of combination therapy (CBT plus fluoxetine) versus antidepressant (fluoxetine) in adults with moderate or severe depression receiving specialist care in the UK. Efficacy data were derived from a systematic review and meta-analysis of RCTs; resource use data were based on expert opinion and published studies. The outcomes of the analysis were the probability of successful treatment (remission and no relapse over 12 months) with remission defined as HRSD-17 ≤ 6 or HRSD-24 ≤ 8 and the QALY, estimated based on vignettes (descriptions of depression-related health states) valued by service users. The time horizon of the analysis was 15 months.

Using a NHS perspective, combination therapy was found to be more costly and more effective than fluoxetine alone, with an ICER of £6,031 per additional successfully treated person (95% CI £2,081 to £27,209), £21,618/QALY (95% CI £7,136 to £118,054/QALY) for adults with moderate depression, and £8,589/QALY (95% CI £2,825 to 483,873/QALY) for adults with severe depression (2020 prices). Results were sensitive to changes in relative efficacy (in terms of remission and relapse). The authors reported that at the NICE upper cost effectiveness threshold of £30,000/QALY (£44,000/QALY in 2020 price), the probability of combination therapy being cost-effective compared with fluoxetine was 0.88 for adults with moderate depression and 0.97 for adults with severe depression. The study is partially applicable to the NICE decision-making context (as the estimation of QALY was not consistent with NICE recommendations) and is characterised by minor limitations.

Combined CBT with citalopram versus CBT alone versus citalopram alone

Koeser 2015 developed an economic model to assess the cost effectiveness of CBT, citalopram and combined therapy of CBT and citalopram in adults with moderate or severe depression receiving specialist care in the UK. Efficacy data for the analysis were derived from systematic screening of a database of RCTs that compared psychological treatments (single or combined) for adults with depression with a control intervention; data were subsequently synthesised using network meta-analysis. Resource use data were based on published estimates of expert opinion and analysis of RCT data. The measure of outcome was the QALY, estimated based on EQ-5D ratings (UK tariff). The time horizon of the analysis was 27 months.

Using a NHS perspective, combination therapy was found to be dominated by CBT, as it was more costly and less effective. CBT was more costly and more effective than citalopram, with an ICER of £22,538/QALY (2020 prices). The probability of each intervention being cost-effective at a cost effectiveness threshold of £28,000/QALY was 0.43 for CBT, 0.37 for citalopram, and 0.20 for combination therapy. Results were sensitive to changes in inclusion criteria for RCTs for acute and follow-up treatment in the systematic review, and the use of SF-6D values (the ICER of CBT versus citalopram reached £36,646/QALY). The study is directly applicable to the NICE decision-making context and is characterised by minor limitations.

Economic model

A decision-analytic model was developed to assess the relative cost effectiveness of interventions of adults with a new episode of more severe depression. The objective of economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix J. This section provides a summary of the methods employed and the results of the economic analysis.

Overview of economic modelling methods

A hybrid decision-analytic model consisting of a decision-tree followed by a three-state Markov model was constructed to evaluate the relative cost effectiveness of a range of pharmacological, psychological, physical and combined interventions for the treatment of a new episode of more severe depression in adults treated in primary care. The time horizon of the analysis was 12 weeks of acute treatment (decision-tree) plus 2 years of follow-up (Markov model). The interventions assessed were determined by the availability of efficacy and acceptability data obtained from the NMAs that were conducted to inform this guideline. The selection of classes of interventions was made based on the following criteria:

- The economic analysis assessed only classes of interventions that were included in the NMA of standardised mean difference (SMD), which was the main clinical outcome, as the committee wanted to be able to assess their clinical effectiveness prior to assessing cost-effectiveness. Moreover, to be assessed in the economic analysis, classes needed to be included in the NMAs of discontinuation (for any reason), response in completers and remission in completers, as these three outcomes informed the economic model.
- Only classes of interventions that had been tested on at least 50 participants (across RCTs) in each of the NMAs of SMD, discontinuation (for any reason), response in completers and remission in completers were included in the economic analysis, as this was the minimum amount of evidence that evidence that a treatment class should have in order to be considered for a practice recommendation. The committee looked at the total size of the evidence base in this area and the large volume of evidence for some treatment classes relative to others, and decided not to consider treatment classes with a small size of evidence base (tested on <50 participants) as there were several treatment classes with a much larger volume of evidence. An exception to this rule was made for classes of interventions that are routinely available in the NHS, that is, such classes were included in the analysis even if they had been tested on fewer than 50 participants in the NMAs mentioned above. For some treatment classes, inclusion in the economic model was not possible as no data were available on one or more NMA outcomes that informed economic modelling. For such classes, additional relevant data were sought by contacting authors of studies already included in the guideline systematic review, so as to enable inclusion of the classes in the respective NMAs and, subsequently, in the economic modelling.
- In addition, only classes with a higher mean effect on the SMD outcome compared with the selected reference treatment (pill placebo) were considered in the economic analysis.

Specific interventions were used as exemplars within each class regarding their intervention costs, so that results of interventions can be extrapolated to other interventions of similar resource intensity within their class. The following interventions [in brackets the classes they belong to] were assessed:

- pharmacological interventions: escitalopram [SSRIs]; lofepramine [TCAs]; duloxetine [SNRIs]; mirtazapine [own class]; trazodone [own class]
- psychological interventions: cCBT without or with minimal support [self-help]; cCBT with support [self-help with support]; individual BA [individual BT]; individual CBT (≥ 15 sessions) [individual CT/CBT]; group CBT (under 15 sessions) [group CT/CBT]; individual problem solving [individual problem solving]; non-directive/supportive/person-centred counselling [individual counselling]; individual IPT [individual IPT]; individual short-term PDPT [individual short-term PDPT]
- physical interventions: supervised high intensity individual exercise [individual exercise]; supervised high intensity group exercise [group exercise]; traditional acupuncture [acupuncture]
- combined interventions: CBT individual (≥ 15 sessions) + escitalopram [combined individual CT/CBT and antidepressant]; traditional acupuncture + escitalopram [combined acupuncture and antidepressant]

- GP care, reflected in the RCT arms of the reference treatment [pill placebo]

The decision-tree component model structure considered the events of discontinuation for any reason and specifically due to intolerable side effects; treatment completion and response reaching remission; treatment completion and response not reaching remission; and treatment completion and inadequate or no response. The Markov component model structure considered the states of remission, depressive episode (due to non-remission or relapse), and death. The specification of the Markov component of the model was based on the relapse prevention model developed for this guideline, details of which are provided in the evidence review C, appendix J.

Efficacy data were derived from the guideline systematic review and NMAs. Data adjusted for bias due to small study size were used in addition to base-case efficacy data, as bias-adjusted analysis suggested the presence of bias due to small study size in the data. Baseline parameters (baseline risk of discontinuation, discontinuation due to side effects, response and remission) were estimated based on a review of naturalistic studies. The measure of outcome of the economic analysis was the number of QALYs gained. Utility data were derived from a systematic review of the literature, and were generated using EQ-5D measurements and the UK population tariff. The perspective of the analysis was that of health and personal social care services. Resource use was based on published literature, national statistics and, where evidence was lacking, the committee's expert opinion. National UK unit costs were used. The cost year was 2020. Model input parameters were synthesised in a probabilistic analysis. This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. A number of one-way deterministic sensitivity analyses was also carried out.

Results have been expressed in the form of Net Monetary Benefits (NMBs). Incremental mean costs and effects (QALYs) of each intervention versus GP care have been presented in the form of cost effectiveness planes. Results of probabilistic analysis have been summarised in the form of cost-effectiveness acceptability frontiers (CEAFs), which show the treatment option with the highest mean NMB over different cost effectiveness thresholds, and the probability that the option with the highest NMB is the most cost-effective among those assessed.

Overview of economic modelling results and conclusions

Individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

The results of the analysis were characterised by considerable uncertainty, as reflected in the wide 95% credible intervals (CrI) around the rankings of interventions. On the other hand, deterministic sensitivity analysis suggested that the results and the ranking of interventions from the most to the least cost-effective were overall robust under different scenarios explored.

Conclusions from the guideline economic analysis refer mainly to people with depression who are treated in primary care for a new depressive episode; however, they may be relevant to people in secondary care as well, given that clinical evidence was derived from a mixture of primary and secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).

Summary of the evidence

Clinical evidence statements for NMA results

This section reports only NMA results that informed the clinical evidence. Detailed NMA findings on all outcomes, including those that informed the economic analysis, are reported in appendix M and supplements B5 and B6.

Critical outcomes

Depression symptomatology - standardised mean difference (SMD) of depression symptom change scores (bias-adjusted analysis)

- Evidence from the NMA shows a clinically important and statistically significant benefit of a mindfulness or meditation group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -3.40, 95% CrI -4.77 to -2.03; 15 participants randomised to mindfulness/meditation group included in this NMA). Mindfulness/meditation group is the highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 1.41 [out of 43], 95% CrI 1 to 4).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a problem solving group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -2.29, 95% CrI -3.49 to -1.10; 47 participants randomised to problem solving group included in this NMA). Problem solving group is the second highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 3.76, 95% CrI 1 to 12).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined yoga group and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.89, 95% CrI -3.95 to 0.10; 15 participants randomised to yoga group + antidepressant included in this NMA). Combined yoga group and antidepressant is the third highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 7.82, 95% CrI 1 to 38).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a peer support group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.35, 95% CrI -2.42 to -0.26; 39 participants randomised to peer support group included in this NMA). Peer support group is the fourth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 9.83, 95% CrI 3 to 30).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined peer support group and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.47, 95% CrI -3.30 to 0.25; 42 participants randomised to peer support group + antidepressant included in this NMA). Combined peer support group and antidepressant is the fifth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 10.42, 95% CrI 2 to 39).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined exercise group and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.37, 95% CrI -2.75 to 0.01; 79 participants randomised to exercise group + antidepressant included in this NMA). Combined exercise group and antidepressant is the sixth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 10.63, 95% CrI 2 to 37).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined individual CBT and antidepressant intervention relative to pill placebo on

depression symptomatology for adults with more severe depression (SMD -1.18, 95% CrI -2.07 to -0.44; 192 participants randomised to individual CBT + antidepressant included in this NMA). Combined individual CBT and antidepressant is the seventh highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 11.09, 95% CrI 4 to 24).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined CBT group and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.23, 95% CrI -2.95 to 0.41; 63 participants randomised to CBT group + antidepressant included in this NMA). Combined CBT group and antidepressant is the eighth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 12.86, 95% CrI 2 to 40).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a psychoeducation group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.01, 95% CrI -2.06 to 0.00; 44 participants randomised to psychoeducation group included in this NMA). Psychoeducation group is the ninth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 14.18, 95% CrI 3 to 36).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a yoga group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -1.04, 95% CrI -2.25 to 0.17; 65 participants randomised to yoga group included in this NMA). Yoga group is the tenth highest ranked intervention for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 14.26, 95% CrI 3 to 39).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a self-help intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.98, 95% CrI -2.52 to 0.39; 344 participants randomised to self-help included in this NMA). Self-help (with no or minimal support) is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 14.99, 95% CrI 3 to 41).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an individual behavioural therapy intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.86, 95% CrI -1.65 to -0.16; 378 participants randomised to individual behavioural therapy included in this NMA). Individual behavioural therapy is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 15.97, 95% CrI 5 to 33).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined individual exercise and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.96, 95% CrI -2.25 to 0.27; 40 participants randomised to individual exercise + antidepressant included in this NMA). Combined individual exercise and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 15.98, 95% CrI 3 to 40).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined bright light therapy and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.86, 95% CrI -1.59 to -0.12; 54 participants randomised to bright light therapy + antidepressant included in this NMA). Combined bright light therapy and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 16.07, 95% CrI 5 to 34).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual problem solving intervention relative to pill placebo on depression

symptomatology for adults with more severe depression (SMD -0.86, 95% CrI -1.75 to 0.01; 367 participants randomised to individual problem solving included in this NMA). Individual problem solving is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 16.22, 95% CrI 5 to 36).

- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined acupuncture and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.78, 95% CrI -1.12 to -0.44; 584 participants randomised to acupuncture + antidepressant included in this NMA). Combined acupuncture and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 16.88, 95% CrI 9 to 26).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an individual CBT intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.78, 95% CrI -1.42 to -0.33; 1044 participants randomised to individual CBT included in this NMA). Individual CBT is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 17.28, 95% CrI 8 to 27).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a non-directive counselling intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.67, 95% CrI -1.53 to 0.15; 404 participants randomised to counselling included in this NMA). Non-directive counselling is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 19.96, 95% CrI 7 to 39).
- Evidence from the NMA suggests a clinically important but not statistically significant benefit of bright light therapy relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.64, 95% CrI -1.60 to 0.29; 32 participants randomised to bright light therapy included in this NMA). Bright light therapy is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 20.89, 95% CrI 6 to 40).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of self-help with support relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.60, 95% CrI -1.61 to 0.54; 267 participants randomised to self-help with support included in this NMA). Self-help with support is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 21.32, 95% CrI 6 to 41).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined IPT and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.66, 95% CrI -2.02 to 0.63; 99 participants randomised to IPT + antidepressant included in this NMA). Combined IPT and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 21.32, 95% CrI 4 to 42).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual short-term psychodynamic psychotherapy intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.58, 95% CrI -1.35 to 0.10; 233 participants randomised to short-term psychodynamic psychotherapy included in this NMA). Individual short-term psychodynamic psychotherapy is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 22.08, 95% CrI 8 to 38).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of IPT relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.45, 95% CrI -1.36 to 0.47; 146 participants randomised to IPT

included in this NMA). IPT is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 25.01, 95% CrI 8 to 41).

- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of acupuncture relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.40, 95% CrI -1.08 to 0.16; 264 participants randomised to acupuncture included in this NMA). Acupuncture is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 26.35, 95% CrI 12 to 39).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a combined individual short-term psychodynamic psychotherapy and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.34, 95% CrI -2.36 to 1.64; 131 participants randomised to short-term psychodynamic psychotherapy + antidepressant included in this NMA). Combined individual short-term psychodynamic psychotherapy and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 26.51, 95% CrI 3 to 43).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a combined psychoeducation group and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.35, 95% CrI -2.13 to 1.35; 27 participants randomised to psychoeducation group + antidepressant included in this NMA). Combined psychoeducation group and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 26.59, 95% CrI 4 to 43).
- Evidence from the NMA shows a statistically significant but not clinically important benefit of mirtazapine relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.35, 95% CrI -0.48 to -0.22; 1884 participants randomised to mirtazapine included in this NMA). Mirtazapine is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 27.04, 95% CrI 20 to 34).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a combined individual behavioural therapy and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.13, 95% CrI -2.82 to 2.71; 22 participants randomised to individual behavioural therapy + antidepressant included in this NMA). Combined individual behavioural therapy and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 28.06, 95% CrI 2 to 43).
- Evidence from the NMA shows a statistically significant but not clinically important benefit of an SNRI relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.32, 95% CrI -0.43 to -0.22; 9538 participants randomised to SNRIs included in this NMA). SNRIs are outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 28.07, 95% CrI 22 to 34).
- Evidence from the NMA shows no benefit of a combined individual relaxation and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD 0.05, 95% CrI -2.82 to 2.96; 10 participants randomised to individual relaxation + antidepressant included in this NMA). Combined individual relaxation and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 29.23, 95% CrI 2 to 43).
- Evidence from the NMA shows a statistically significant but not clinically important benefit of a TCA relative to pill placebo on depression symptomatology for adults with more

severe depression (SMD -0.29, 95% CrI -0.50 to -0.05; 4524 participants randomised to TCAs included in this NMA). TCAs are outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 29.34, 95% CrI 21 to 37).

- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a music therapy group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.14, 95% CrI -1.69 to 1.41; 12 participants randomised to music therapy group included in this NMA). Music therapy group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 29.54, 95% CrI 5 to 43).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a CBT group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.26, 95% CrI -1.12 to 0.60; 165 participants randomised to CBT group included in this NMA). CBT group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 29.59, 95% CrI 11 to 42).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of an exercise group intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.19, 95% CrI -1.20 to 0.87; 106 participants randomised to exercise group included in this NMA). Execise group is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 30.60, 95% CrI 10 to 42).
- Evidence from the NMA shows a statistically significant but not clinically important benefit of an SSRI relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.24, 95% CrI -0.32 to -0.16; 22,018 participants randomised to SSRIs included in this NMA). SSRIs are outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 31.21, 95% CrI 25 to 37).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of an individual exercise intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.13, 95% CrI -1.24 to 1.10; 298 participants randomised to individual exercise included in this NMA). Individual exercise is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 31.75, 95% CrI 9 to 43).
- Evidence from the NMA shows no benefit of a combined non-directive counselling and antidepressant intervention relative to pill placebo on depression symptomatology for adults with more severe depression (SMD 0.21, 95% CrI -2.52 to 2.96; 57 participants randomised to counselling + antidepressant included in this NMA). Combined non-directive counselling and antidepressant is outside the top-10 highest ranked interventions for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 32.21, 95% CrI 4 to 43).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of trazodone relative to pill placebo on depression symptomatology for adults with more severe depression (SMD -0.13, 95% CrI -0.29 to 0.04; 1072 participants randomised to trazodone included in this NMA). Trazodone is ranked third from bottom (only above placebo and waitlist) for clinical efficacy as measured by SMD of depression symptom change scores (mean rank 34.14, 95% CrI 27 to 40).

Response in those randomised

- Evidence from the NMA shows a clinically important and statistically significant benefit of a mindfulness or meditation group intervention relative to pill placebo on response (in

those randomised) for adults with more severe depression (15 participants randomised to mindfulness/meditation group included in this NMA). Mindfulness/meditation group is the highest ranked intervention for response in those randomised (mean rank 1.48 [out of 38], 95% CrI 1 to 4).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined yoga group and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (15 participants randomised to yoga group + antidepressant included in this NMA). Combined yoga group and antidepressant is the second highest ranked intervention for response in those randomised (mean rank 6.91, 95% CrI 1 to 32).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined individual exercise and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (40 participants randomised to individual exercise + antidepressant included in this NMA). Combined individual exercise and antidepressant is the third highest ranked intervention for response in those randomised (mean rank 8.25, 95% CrI 2 to 25).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined individual CBT and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (158 participants randomised to individual CBT + antidepressant included in this NMA). Combined individual CBT and antidepressant is the fourth highest ranked intervention for response in those randomised (mean rank 8.39, 95% CrI 2 to 21).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a peer support group intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (39 participants randomised to peer support group included in this NMA). Peer support group is the fifth highest ranked intervention for response in those randomised (mean rank 9.03, 95% CrI 2 to 29).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined peer support group and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (42 participants randomised to peer support group + antidepressant included in this NMA). Combined peer support group and antidepressant is the sixth highest ranked intervention for response in those randomised (mean rank 9.64, 95% CrI 1 to 35).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined exercise group and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (79 participants randomised to exercise group + antidepressant included in this NMA). Combined exercise group and antidepressant is the seventh highest ranked intervention for response in those randomised (mean rank 10.21, 95% CrI 2 to 33).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined CBT group and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (20 participants randomised to CBT group + antidepressant included in this NMA). Combined CBT group and antidepressant is the eighth highest ranked intervention for response in those randomised (mean rank 10.36, 95% CrI 2 to 36).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined individual behavioural therapy and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (10 participants randomised to individual behavioural therapy + antidepressant included in this NMA). Combined individual behavioural therapy and antidepressant is the ninth highest ranked intervention for response in those randomised (mean rank 12.55, 95% CrI 1 to 38).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an individual CBT intervention relative to pill placebo on response (in those randomised)

for adults with more severe depression (779 participants randomised to individual CBT included in this NMA). Individual CBT is the tenth highest ranked intervention for response in those randomised (mean rank 13.92, 95% CrI 6 to 24).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined bright light therapy and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (54 participants randomised to bright light therapy + antidepressant included in this NMA). Combined bright light therapy and antidepressant is outside the top-10 highest ranked interventions for response in those randomised (mean rank 14.44, 95% CrI 3 to 36).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual behavioural therapy intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (368 participants randomised to individual behavioural therapy included in this NMA). Individual behavioural therapy is outside the top-10 highest ranked interventions for response in those randomised (mean rank 14.87, 95% CrI 4 to 35).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a self-help intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (168 participants randomised to self-help included in this NMA). Self-help (with no or minimal support) is outside the top-10 highest ranked interventions for response in those randomised (mean rank 15.07, 95% CrI 4 to 34).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual short-term psychodynamic psychotherapy intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (217 participants randomised to short-term psychodynamic psychotherapy included in this NMA). Individual short-term psychodynamic psychotherapy is outside the top-10 highest ranked interventions for response in those randomised (mean rank 16.16, 95% CrI 5 to 32).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined acupuncture and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (553 participants randomised to acupuncture + antidepressant included in this NMA). Combined acupuncture and antidepressant is outside the top-10 highest ranked interventions for response in those randomised (mean rank 16.29, 95% CrI 10 to 23).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of self-help with support relative to pill placebo on response (in those randomised) for adults with more severe depression (274 participants randomised to self-help with support included in this NMA). Self-help with support is outside the top-10 highest ranked interventions for response in those randomised (mean rank 17.34, 95% CrI 6 to 33).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined non-directive counselling and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (52 participants randomised to counselling + antidepressant included in this NMA). Combined non-directive counselling and antidepressant outside the top-10 highest ranked interventions for response in those randomised (mean rank 17.97, 95% CrI 3 to 38).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of IPT relative to pill placebo on response (in those randomised) for adults with more severe depression (61 participants randomised to IPT included in this NMA). IPT is outside the top-10 highest ranked interventions for response in those randomised (mean rank 18.9, 95% CrI 5 to 36).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual problem solving intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (338 participants randomised to individual problem solving included in this NMA). Individual problem solving is outside the

top-10 highest ranked interventions for response in those randomised (mean rank 19.43, 95% CrI 5 to 36).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of bright light therapy relative to pill placebo on response (in those randomised) for adults with more severe depression (32 participants randomised to bright light therapy included in this NMA). Bright light therapy is outside the top-10 highest ranked interventions for response in those randomised (mean rank 20.52, 95% CrI 2 to 38).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a music therapy group intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (12 participants randomised to music therapy group included in this NMA). Music therapy group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 21.57, 95% CrI 5 to 38).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a non-directive counselling intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (421 participants randomised to counselling included in this NMA). Non-directive counselling is outside the top-10 highest ranked interventions for response in those randomised (mean rank 22.14, 95% CrI 6 to 37).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined self-help and antidepressant intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (79 participants randomised to self-help + antidepressant included in this NMA). Combined self-help and antidepressant is outside the top-10 highest ranked interventions for response in those randomised (mean rank 22.42, 95% CrI 3 to 38).
- Evidence from the NMA shows a clinically important and statistically significant benefit of mirtazapine relative to pill placebo on response (in those randomised) for adults with more severe depression (2629 participants randomised to mirtazapine included in this NMA). Mirtazapine is outside the top-10 highest ranked interventions for response in those randomised (mean rank 22.98, 95% CrI 18 to 28).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a yoga group intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (45 participants randomised to yoga group included in this NMA). Yoga group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 23.32, 95% CrI 5 to 38).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a TCA relative to pill placebo on response (in those randomised) for adults with more severe depression (5437 participants randomised to TCAs included in this NMA). TCAs are outside the top-10 highest ranked interventions for response in those randomised (mean rank 23.45, 95% CrI 18 to 29).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an SNRI relative to pill placebo on response (in those randomised) for adults with more severe depression (10,469 participants randomised to SNRIs are included in this NMA). SNRIs are outside the top-10 highest ranked interventions for response in those randomised (mean rank 24.03, 95% CrI 19 to 29).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a CBT group intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (155 participants randomised to CBT group are included in this NMA). CBT group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 24.44, 95% CrI 7 to 37).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of acupuncture relative to pill placebo on response (in those randomised) for adults with more severe depression (217 participants randomised to acupuncture included in this

NMA). Acupuncture is outside the top-10 highest ranked interventions for response in those randomised (mean rank 24.51, 95% CrI 6 to 38).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual exercise intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (273 participants randomised to individual exercise included in this NMA). Individual exercise is outside the top-10 highest ranked interventions for response in those randomised (mean rank 24.77, 95% CrI 10 to 37).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an exercise group intervention relative to pill placebo on response (in those randomised) for adults with more severe depression (126 participants randomised to exercise group included in this NMA). Exercise group is outside the top-10 highest ranked interventions for response in those randomised (mean rank 25.93, 95% CrI 11 to 37).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an SSRI relative to pill placebo on response (in those randomised) for adults with more severe depression (26,961 participants randomised to SSRIs included in this NMA). SSRIs are outside the top-10 highest ranked interventions for response in those randomised (mean rank 26.53, 95% CrI 22 to 31).
- Evidence from the NMA shows a clinically important and statistically significant benefit of trazodone relative to pill placebo on response (in those randomised) for adults with more severe depression (1181 participants randomised to trazodone included in this NMA). Trazodone is outside the top-10 highest ranked interventions for response in those randomised (mean rank 28.71, 95% CrI 24 to 33).

Remission in those randomised

- Evidence from the NMA shows a clinically important and statistically significant benefit of long-term psychodynamic psychotherapy relative to pill placebo on remission (in those randomised) for adults with more severe depression (90 participants randomised to long-term psychodynamic psychotherapy included in this NMA). Long-term psychodynamic psychotherapy is the highest ranked intervention for remission in those randomised (mean rank 3.87 [out of 35], 95% CrI 1 to 17).
- Evidence from the NMA shows a clinically important and statistically significant benefit of a combined long-term psychodynamic psychotherapy and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (91 participants randomised to long-term psychodynamic psychotherapy + antidepressant included in this NMA). Combined long-term psychodynamic psychotherapy and antidepressant is the second highest ranked intervention for remission in those randomised (mean rank 5.54, 95% CrI 1 to 24).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a problem solving group intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (58 participants randomised to problem solving group included in this NMA). Problem solving group is the third highest ranked intervention for remission in those randomised (mean rank 8.18, 95% CrI 1 to 31).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined bright light therapy and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (54 participants randomised to bright light therapy + antidepressant included in this NMA). Combined bright light therapy and antidepressant is the fourth highest ranked intervention for remission in those randomised (mean rank 10.09, 95% CrI 2 to 28).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined IPT and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (16 participants randomised to IPT + antidepressant included in this NMA). Combined IPT and antidepressant is the fifth

highest ranked intervention for remission in those randomised (mean rank 11.00, 95% CrI 1 to 32).

- Evidence from the NMA shows a clinically important but not statistically significant benefit of a self-help intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (349 participants randomised to self-help included in this NMA). Self-help (with no or minimal support) is the sixth highest ranked intervention for remission in those randomised (mean rank 11.28, 95% CrI 2 to 29).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual short-term psychodynamic psychotherapy intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (129 participants randomised to short-term psychodynamic psychotherapy included in this NMA). Individual short-term psychodynamic psychotherapy is the seventh highest ranked intervention for remission in those randomised (mean rank 12.50, 95% CrI 2 to 30).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined exercise group and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (134 participants randomised to exercise group + antidepressant included in this NMA). Combined exercise group and antidepressant is the eighth highest ranked intervention for remission in those randomised (mean rank 13.42, 95% CrI 3 to 30).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of IPT relative to pill placebo on remission (in those randomised) for adults with more severe depression (63 participants randomised to IPT included in this NMA). IPT is the ninth highest ranked intervention for remission in those randomised (mean rank 13.48, 95% CrI 2 to 32).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual behavioural therapy intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (354 participants randomised to individual behavioural therapy included in this NMA). Individual behavioural therapy is the tenth highest ranked intervention for remission in those randomised (mean rank 13.84, 95% CrI 2 to 32).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual problem solving intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (232 participants randomised to individual problem solving included in this NMA). Individual problem solving is outside the top-10 highest ranked interventions for remission in those randomised (mean rank 13.96, 95% CrI 2 to 33).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined individual CBT and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (117 participants randomised to individual CBT + antidepressant included in this NMA). Combined individual CBT and antidepressant is outside the top-10 highest ranked interventions for remission in those randomised (mean rank 14.17, 95% CrI 3 to 31).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of bright light therapy relative to pill placebo on remission (in those randomised) for adults with more severe depression (32 participants randomised to bright light therapy included in this NMA). Bright light therapy is outside the top-10 highest ranked interventions for remission in those randomised (mean rank 14.77, 95% CrI 2 to 33).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined non-directive counselling and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (13 participants randomised to counselling + antidepressant included in this NMA). Combined non-directive counselling and antidepressant is outside the top-10 highest ranked interventions for remission in those randomised (mean rank 16.43, 95% CrI 1 to 34).

- Evidence from the NMA shows a clinically important and statistically significant benefit of a TCA relative to pill placebo on remission (in those randomised) for adults with more severe depression (1747 participants randomised to TCAs included in this NMA). TCAs are outside the top-10 highest ranked interventions for remission in those randomised (mean rank 17.28, 95% CrI 9 to 27).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of acupuncture relative to pill placebo on remission (in those randomised) for adults with more severe depression (122 participants randomised to acupuncture included in this NMA). Acupuncture is outside the top-10 highest ranked interventions for remission in those randomised (mean rank 18.64, 95% CrI 2 to 33).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an SNRI relative to pill placebo on remission (in those randomised) for adults with more severe depression (8727 participants randomised to SNRIs included in this NMA). SNRIs are outside the top-10 highest ranked interventions for remission in those randomised (mean rank 18.76, 95% CrI 12 to 25).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual CBT intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (451 participants randomised to individual CBT included in this NMA). Individual CBT is outside the top-10 highest ranked interventions for remission in those randomised (mean rank 18.84, 95% CrI 5 to 32).
- Evidence from the NMA shows a clinically important and statistically significant benefit of mirtazapine relative to pill placebo on remission (in those randomised) for adults with more severe depression (726 participants randomised to mirtazapine included in this NMA). Mirtazapine is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 19.15, 95% CrI 12 to 26).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined acupuncture and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (112 participants randomised to acupuncture + antidepressant included in this NMA). Combined acupuncture and antidepressant is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 19.19, 95% CrI 4 to 33).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of self-help with support relative to pill placebo on remission (in those randomised) for adults with more severe depression (416 participants randomised to self-help with support included in this NMA). Self-help with support is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 19.56, 95% CrI 5 to 32).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an exercise group intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (104 participants randomised to exercise group included in this NMA). Exercise group is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 20.59, 95% CrI 4 to 34).
- Evidence from the NMA shows a clinically important and statistically significant benefit of an SSRI relative to pill placebo on remission (in those randomised) for adults with more severe depression (15,203 participants randomised to SSRIs included in this NMA). SSRIs are outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 21.81, 95% CrI 16 to 27).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of a combined individual exercise and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (55 participants randomised to individual exercise + antidepressant included in this NMA).

Combined individual exercise and antidepressant is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 22.13, 95% CrI 4 to 34).

- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a CBT group intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (65 participants randomised to CBT group included in this NMA). CBT group is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 22.30, 95% CrI 4 to 34).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a non-directive counselling intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (124 participants randomised to counselling included in this NMA). Non-directive counselling is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 22.35, 95% CrI 4 to 34).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a yoga group intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (15 participants randomised to yoga group included in this NMA). Yoga group is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU (mean rank 22.36, 95% CrI 3 to 35).
- Evidence from the NMA shows a clinically important but not statistically significant benefit of an individual exercise intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (336 participants randomised to individual exercise included in this NMA). Individual exercise is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU and sham acupuncture (mean rank 22.69, 95% CrI 6 to 33).
- Evidence from the NMA shows neither a clinically important nor statistically significant benefit of a combined CBT group and antidepressant intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression (34 participants randomised to CBT group + antidepressant included in this NMA). Combined CBT group and antidepressant is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU and sham acupuncture (mean rank 22.90, 95% CrI 3 to 34).
- Evidence from the NMA shows a clinically important and statistically significant benefit of trazodone relative to pill placebo on remission (in those randomised) for adults with more severe depression (742 participants randomised to trazodone included in this NMA). Trazodone is outside the top-10 highest ranked interventions for remission in those randomised and is ranked below TAU and sham acupuncture (mean rank 23.11, 95% CrI 16 to 29).
- Evidence from the NMA shows a lower effect of a short-term psychodynamic psychotherapy group intervention relative to pill placebo on remission (in those randomised) for adults with more severe depression, and this difference is clinically important and statistically significant (24 participants randomised to short-term psychodynamic psychotherapy group included in this NMA). Short-term psychodynamic psychotherapy group is ranked bottom for remission in those randomised, and is ranked below TAU, sham acupuncture, pill placebo and waitlist (mean rank 34.32, 95% CrI 28 to 35).

Clinical evidence statements for pairwise meta-analysis results of studies included in the NMA

Important, but not critical, outcomes

Quality of life

- Single-RCT evidence (N=74) shows a clinically important and statistically significant benefit of an individual CBT intervention relative to self-help with support on quality of life for adults with more severe depression.
- Single-RCT evidence (N=38) shows a clinically important and statistically significant benefit of a combined individual CBT and SSRI intervention relative to TAU on quality of life for adults with more severe depression.
- Single-RCT evidence (N=71) shows a clinically important and statistically significant benefit of a self-help intervention relative to no treatment on quality of life for adults with more severe depression.
- Single-RCT evidence (N=127) shows a clinically important and statistically significant benefit of an individual short-term psychodynamic psychotherapy intervention relative to self-help with support on quality of life for adults with more severe depression.
- Single-RCT evidence (N=70) shows a clinically important and statistically significant benefit of an individual exercise intervention relative to no treatment on quality of life for adults with more severe depression.
- Single-RCT evidence (N=43) shows a clinically important and statistically significant benefit of a yoga group intervention relative to waitlist on quality of life for adults with more severe depression.

Personal, social and occupational functioning

- Single-RCT evidence (N=137) shows a clinically important and statistically significant benefit of an individual CBT intervention relative to no treatment on functional impairment for adults with more severe depression.
- Single-RCT evidence (N=121) shows a clinically important and statistically significant benefit of an individual problem solving intervention relative to attention placebo on functional impairment for adults with more severe depression.
- Single-RCT evidence (N=25) shows a clinically important and statistically significant benefit of an individual problem solving intervention relative to non-directive counselling on functional impairment for adults with more severe depression.
- Single-RCT evidence (N=258) shows a clinically important and statistically significant benefit of a non-directive counselling intervention relative to no treatment on functional impairment for adults with more severe depression.
- Single-RCT evidence (N=31) shows a clinically important and statistically significant benefit of a combined IPT and SNRI intervention relative to SNRI-only on global functioning for adults with more severe depression.
- Single-RCT evidence (N=183) shows a clinically important and statistically significant benefit of a self-help intervention relative to waitlist on functional impairment for adults with more severe depression.
- Single-RCT evidence (N=50) shows a clinically important and statistically significant benefit of self-help with support relative to waitlist on sleeping difficulties for adults with more severe depression.
- Single-RCT evidence (N=93) shows a clinically important and statistically significant benefit of an individual short-term psychodynamic psychotherapy intervention relative to individual CBT on interpersonal problems for adults with more severe depression.

- Single-RCT evidence (N=127) shows a clinically important and statistically significant benefit of an individual short-term psychodynamic psychotherapy intervention relative to self-help with support on interpersonal problems for adults with more severe depression.
- Single-RCT evidence (N=210) shows a clinically important and statistically significant benefit of an SSRI relative to placebo on sleeping difficulties for adults with more severe depression.

Clinical evidence statements for pairwise meta-analysis of couple interventions (not included in NMA)

Comparison 1: Behavioural couples therapy versus waitlist

Critical outcomes

Depression symptoms (change score)

- Very low quality evidence from one RCT (N=30) shows a clinically important and statistically significant benefit of behavioural couples therapy relative to waitlist on the change in depression symptoms from baseline to endpoint for adults with more severe depression and with relationship problems.

Important, but not critical, outcomes

Marital adjustment (change score)

- Very low quality evidence from one RCT (N=30) shows a clinically important and statistically significant benefit of behavioural couples therapy relative to waitlist on the change in marital adjustment from baseline to endpoint for adults with more severe depression and with relationship problems.

Comparison 2: Behavioural couples therapy versus CBT individual

Critical outcomes

Depression symptoms (change score)

- Very low quality evidence from one RCT (N=30) shows no significant difference between behavioural couples therapy and an individual CBT intervention on the change in depression symptoms from baseline to endpoint for adults with more severe depression and with relationship problems.

Important, but not critical, outcomes

Marital adjustment (change score)

- Very low quality evidence from one RCT (N=30) shows a clinically important and statistically significant benefit of behavioural couples therapy relative to an individual CBT intervention on the change in marital adjustment from baseline to endpoint for adults with more severe depression and with relationship problems.

Comparison 3: CBT individual versus waitlist

Critical outcomes

Depression symptoms (change score)

- Low quality evidence from one RCT (N=30) shows a clinically important and statistically significant benefit of an individual CBT intervention relative to waitlist on the change in depression symptoms from baseline to endpoint for adults with more severe depression and with relationship problems.

Important, but not critical, outcomes

Marital adjustment (change score)

- Very low quality evidence from one RCT (N=30) shows no benefit of an individual CBT intervention relative to waitlist on the change in marital adjustment from baseline to endpoint for adults with more severe depression and with relationship problems.

Economic evidence statements

- Evidence from 1 single UK study conducted alongside a RCT (N = 691) indicates that computerised CBT with support is unlikely to be cost-effective compared with treatment as usual in adults with a new episode of more severe depression. The evidence is directly applicable to the UK context and is characterised by minor limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N=103) and a preference trial (N= 220) is inconclusive regarding the cost effectiveness of non-directive counselling versus antidepressants in adults with a new episode of more severe depression. The study is partially applicable to the NICE decision-making context and is characterised by potentially serious limitations.
- Evidence from subgroup analysis from a single UK study conducted alongside a RCT (N = 655) suggests that sertraline is very likely to be cost-effective compared with placebo in adults with a new episode of more severe depression. The evidence is directly applicable to the UK context and is characterised by minor limitations.
- Evidence from 2 model-based UK studies suggests that escitalopram is more cost-effective than citalopram and duloxetine (assessed in 1 of the studies) in adults with a new episode of more severe depression. The evidence is directly applicable to the NICE decision-making context but is characterised by potentially serious limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N=295) suggests that sertraline is likely to be cost-effective compared with duloxetine in adults with a new episode of more severe depression. The study is directly applicable to the NICE decision-making context and is characterised by potentially serious limitations.
- Evidence from 1 single UK study conducted alongside a RCT (N=197) suggests that mirtazapine is likely to be cost-effective compared with paroxetine in adults with a new episode of more severe depression. The study is directly applicable to the NICE decision-making context and is characterised by potentially serious limitations.
- Evidence from 1 model-based UK study suggests that duloxetine is likely the most cost-effective option when compared with SSRIs, venlafaxine and mirtazapine in adults with a new episode of more severe depression. The study is directly applicable to the NICE decision-making context but is characterised by potentially serious limitations.
- Evidence from 1 model-based UK study suggests that venlafaxine may be more cost-effective than fluoxetine and amitriptyline in adults with a new episode of more severe depression. However, the study is partially applicable to the NICE decision-making context and is characterised by very serious limitations.

- Evidence from 1 model-based UK study suggests that combination therapy (CBT and fluoxetine) is likely to be more cost-effective versus pharmacological treatment (fluoxetine) alone in adults with a new episode of more severe depression. The evidence is partially applicable to the NICE decision-making context and is characterised by minor limitations.
- Evidence from 1 model-based UK study suggests that CBT is likely to be more cost-effective than combination therapy (CBT and citalopram) in adults with a new episode of more severe depression. The evidence on the cost effectiveness between CBT and pharmacological therapy (citalopram) is inconclusive. The evidence is directly applicable to the NICE decision-making context and is characterised by minor limitations.
- Evidence from the guideline economic modelling suggests that individual problem solving is likely to be the most cost-effective option for the treatment of new episodes of more severe depression in adults, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. This evidence refers mainly to people treated in primary care for a new depressive episode; however, it may be relevant to people treated in secondary care as well, given that clinical evidence was derived from a mixture of primary and secondary care settings. The economic analysis is directly applicable to the NICE decision-making context and is characterised by minor limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify the most effective and cost-effective treatments for more severe depression and the committee chose depression symptomatology (measured as the standardised mean difference, SMD, of depression symptom change scores at treatment endpoint), remission (in those randomised) and response (in those randomised) as critical outcomes to provide an indication of clinical effectiveness. Discontinuation due to side effects and discontinuation for any reason were also chosen as critical outcomes, as indicators of the tolerability and acceptability of treatments, but results for these outcomes were used as part of the economic modelling (along with remission and response in completers) and were not reviewed by the committee separately.

In addition to the critical, depression-specific, outcomes the committee prioritised 2 important outcomes – these were quality of life and personal, social and occupational functioning. These were selected to determine if treatments for depression led to improved quality of life, and helped overcome difficulties in sleep, participation in employment, and carrying out activities of daily living. These were selected as important and not critical outcomes as the committee were aware that there was likely to be less evidence for these outcomes. The committee recognised that although these outcomes were very important to people with depression, as they would not be available for all interventions they would be less useful to the committee to make recommendations.

The critical outcomes were assessed at treatment endpoint, but in order to determine if treatments for depression had longer term benefits, follow-up measurements of depression symptomatology, remission and response were also analysed. Outcomes at these additional timepoints were also assessed by the committee as part of their decision-making process. However, the committee recognised that although these longer-term outcomes were very important to people with depression, as they would not be available for all interventions they would be less useful to the committee to make recommendations.

For each outcome, the committee decided to consider only treatment classes that had been tested on at least 50 participants across the RCTs included in the respective NMA, after looking at the total size of the evidence base on treatments for a new episode of more severe depression and noticing that there were several treatment classes with a much larger volume of evidence.

The quality of the evidence

The trials included for this evidence review were individually assessed using the Cochrane risk of bias tool (version 1.0), and the summarised quality of the evidence is presented in the evidence review. Overall, the majority of domains were rated as at low risk, or unclear risk of bias, with the exception of selective reporting bias, and other bias (which included potential conflict of interest based on the source of funding).

Regarding the outcomes considered in the clinical analysis, the between-trial heterogeneity relative to the size of the intervention effect estimates was moderate for the SMD of depression symptom scores, response in those randomised, and remission in those randomised. Some evidence of inconsistency was identified in all outcomes considered in the clinical analysis. In the analysis of the SMD of depression symptom scores there was evidence of bias associated with small study size. The bias adjusted model resulted in small to moderate changes in the relative effects of all treatment classes versus pill placebo (reference treatment) and also had a moderate impact on some class rankings. The committee took this information into account when interpreting the results.

Regarding the outcomes that informed the economic analysis, relative to the size of the intervention effect estimates, the between trial heterogeneity was found to be moderate for discontinuation due to any reason, discontinuation due to side effects from medication in those discontinuing treatment, and response in completers, and small for remission in completers. Some evidence of inconsistency was identified for discontinuation due to any reason, discontinuation due to side effects from medication in those discontinuing treatment, and remission in completers. There was also evidence of bias associated with small study size identified for both discontinuation due to any reason and response in completers.

The sensitivity analysis on the SMD outcome conducted to explore the transitivity assumption of participants in pharmacological and non-pharmacological studies found that there were some differences in the results when the pharmacological trials were excluded from analysis, however these were not substantial and thus the transitivity assumptions are acceptable.

The post-hoc sub-group analysis on the SMD outcome that included only studies at low risk for the attrition domain of the Cochrane risk-of-bias tool showed no substantial difference in treatment effects compared with the base-case analysis. This suggested that bias from attrition was unlikely to be an effect modifier in this population.

The committee noted that the effectiveness of psychological interventions may depend on clinicians' training, expertise and previous experience with specific treatments, as well as patients' needs, preferences and experiences with previous treatments for depression. The committee acknowledged that these factors may have affected, to some extent, the efficacy of treatments in the RCTs included in the NMAs, and also patient outcomes in clinical practice. These issues were considered when interpreting the available evidence, but also when formulating reocmmendations.

A threshold analysis was originally planned, to assess the robustness of the intervention recommendations to potential limitations in the evidence synthesised in NMAs. Threshold analysis suggests by how much effects that have been estimated in the NMA need to change before recommendations change, and whether such changes might potentially occur due to bias in the evidence. The NICE Guidelines Technical Support Unit (TSU) attended committee discussions on the rationale for recommendations and noted that, in addition to the results of

the NMA, the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The TSU advised that as it was difficult to identify a clear decision rule to link the recommendations directly to the NMA results, it was not feasible or helpful to conduct a threshold analysis. The committee agreed with the observation that recommendations were based on a pragmatic approach utilising their clinical experience and the need for inclusivity; and their wish for pragmatic recommendations tailored to individual needs and preferences. Therefore they agreed that threshold analysis would not add value to decision making.

Benefits and harms

The committee discussed the results of the clinical and economic analyses and used this information to draft recommendations relating to the use of specific interventions for the treatment of more severe depression. When reviewing the evidence from the network meta-analysis, the committee were aware that a number of important and well-known, often pragmatic, trials were excluded from the NMA, typically because the samples in the trials were <80% first-line treatment or <80% non-chronic depression. These were stipulations of the review protocol in order to create a homogenous data set, but the committee used their knowledge of these studies in the round when interpreting the evidence from the systematic review and making recommendations. The committee were particularly mindful of the UK-based psychological treatment studies (or multicentre studies that included a UK centre) that had been excluded on this basis, due to the relevance to the NHS context. For more severe depression, the committee's knowledge of the results of these trials (Blackwell et al. 2015; Brabyn et al. 2016; Delgadillo et al. 2015; Dowrick et al. 2000; Ekers et al. 2011; Kessler et al. 2009; Macaskill & Macaskill, 1996; MacPherson et al. 2013; Martin et al. 2001; Mead et al. 2015; Proudfoot et al. 2003, 2004; Richards et al. 2016; Russell et al. 2019, 2020; Sugg et al. 2018; Teasdale et al. 1984; Watkins et al. 2012) was brought to bear when interpreting the results of the NMA. The results of these studies were broadly consistent with the evidence from the systematic review, and the committee therefore took this into consideration when making their recommendations.

The committee reviewed the results of the bias-adjusted NMA for more severe depression for the outcome of SMD, compared to pill placebo. The committee noted that the point estimate for the majority of intervention classes showed an improvement in depression symptoms, but that most also had very wide 95% credible intervals which crossed zero, and therefore there was uncertainty around the effectiveness. The committee noted that there were some classes for which there was evidence from more than 50 participants, and credible intervals that did not cross zero – these were individual cognitive and cognitive behavioural therapies (CT/CBT), individual behavioural therapy, pharmacological treatments (SSRIs, TCAs, SNRIs, mirtazapine), and combination therapy with individual CT/CBT plus antidepressants, acupuncture plus antidepressants, and light therapy plus antidepressants. The committee noted that the credible intervals for the pharmacological therapies were all very narrow, and that this was due to the fact that these results were based on large populations from multiple studies and therefore there was less uncertainty around these results, whereas the evidence for some of the other interventions was based on far fewer participants. The committee agreed that these results were in-line with their clinical experience that CBT, behavioural therapies and pharmacological therapies were all effective to treat more severe depression, and that it was likely that combination treatments with antidepressants were likely to be effective as well, and might lead to additional benefits, over and above the effect of a single intervention. The committee agreed that there was very litte to differentiate between the other classes based on the bias-adjusted SMD evidence alone. The committee also reviewed the NMA ranking for the classes of interventions but noted the very wide credible intervals in the ranks provided, and agreed this did not provide any additional information to help them distinguish between the classes.

The committee discussed the bias-adjusted SMD results for individual interventions within each class and noted there was evidence that some interventions were effective, even when the class effect did not show a significant difference from pill placebo. For example, self-help (both with and without support) had credible intervals that crossed zero but the individual interventions of cognitive bibliotherapy and computerised CBT (with or without support) showed a significant effect compared to pill placebo. Likewise, the classes of individual problem-solving, non-directive counselling, short-term psychodynamic psychotherapy, combination therapy of group CT/CBT with antidepressants, combination therapy of IPT with antidepressants, and combination therapy of group exercise with antidepressants were non-significant, but individual interventions within these classes showed significant benefit.

The committee next reviewed the results for response and remission in those randomised. For the outcome of response, the committee noted that the results were similar to those seen for the SMD outcome, with most classes of intervention offering some benefits but the majority of the credible intervals crossing zero, and the classes of interventions for which there was evidence from more than 50 participants, and credible intervals that did not cross zero were also similar to the results seen for SMD. These classes were individual CT/CBT and pharmacological treatments (SSRIs, TCAs, SNRIs, mirtazapine, trazodone), and the combinations of CT/CBT with antidepressants and acupuncture with antidepressants. For the outcome of remission, the results were slightly different: all the pharmacological treatments (SSRIs, TCAs, SNRIs, mirtazapine, trazodone) still showed benefits compared to pill placebo, with narrow credible intervals that did not cross zero, but the only psychological intervention that fulfilled this was individual long-term psychodynamic therapy (PDPT), or the combination of long-term PDPT with antidepressants, although the evidence for both these classes was based on a population of 90 people.

The committee discussed the sensitivity analysis conducted to determine if the inclusion of pharmacological trials impacted on the results seen for psychological, psychosocial and physical therapies. It was noted that exclusion of the pharmacological studies had small effects on some SMDs compared to treatment as usual, and that in this analysis the confidence intervals for individual CT/CBT widened so that they crossed zero. However, the committee agreed that these small changes indicated that the NMA analysis including the pharmacological trials was robust and that this would not impact on their recommendations.

The evidence for the outcomes of quality of life and functioning outcomes, and follow-up of depression outcomes were, as described above, presented as pairwise analyses. The committee reviewed the outcomes where a clinically important and statistically significant difference had been identified, but noted that the results were all from single studies, many of which were small (some with fewer than 50 participants). For the studies with more than 50 participants and the outcome of quality of life, the committee noted that there was some evidence of benefit for individual CBT, CBT plus antidepressants, self-help and individual exercise compared to no treatment/treatment as usual/waitlist. For the functional outcomes there was evidence of benefit for individual CBT, individual problem-solving, non-directive counselling, self-help (with or without support) and SSRIs compared to no treatment/attention placebo/waitlist/pill placebo. Comparisons of individual STPP with self-help with support and individual CBT suggested there may be benefits with STPP, and one comparison of individual problem-solving with non-directive counselling, suggested benefits of problem-solving. The committee agreed that these results confirmed that there may be additional benefits on quality of life and functional outcomes with some of the interventions for depression that had shown benefit for the critical outcomes, and this provided reassurance, but there was not enough evidence on these important outcomes to alter their recommendations.

There were very few comparisons from the follow-up data on depression outcomes that showed a clinically important and statistically significant difference. There was some very limited evidence from single studies that individual behavioural therapy led to improved rates of remission at 9 months compared to no treatment and improved rates of response and

remission at 8 months compared to SSRIs, and similarly that individual CBT led to an improvement in depression symptoms at 12 months, compared to antidepressants. There was also very limited evidence from small, single studies that self-help may lead to benefits at 6 and 9 months' follow-up compared to no treatment or treatment as usual. The committee agreed that this very limited evidence provided some reassurance that classes of interventions that had shown beneficial results at endpoint, may have beneficial results at follow-up as well, but that there was not enough evidence to develop recommendations based on follow-up data alone.

The next piece of clinical evidence the committee reviewed was the summary of the differences between the pairwise analysis and the NMA results. It was noted that the number of comparisons where there was a significant difference was small (11%), and in the majority of cases that difference was in the magnitude of the effect. The committee noted that for three interventions, the magnitude was much greater using the pairwise analysis: CBT individual compared to SNRIs, non-directive counselling versus no treatment, and STPP versus self-help with support, but that the confidence intervals for all these comparisons were very wide. The committee agreed that these differences should be considered when making their recommendations.

The committee noted that the evidence for the subgroup analysis of older versus younger people showed no difference between the groups for any of the comparisons and so no specific recommendations were made for people of different ages.

Finally, the committee considered the pairwise analysis of behavioural couples therapy for people with depression and problems in the relationship with their partner. This evidence was based on a small, single study which indicated that compared to waitlist, couples' therapy demonstrated benefits in terms of depression symptoms and marital adjustment, but when compared to CBT it did not show a benefit in depression sympyoms, but did with marital adjustment. CBT compared to waitlist demonstrated benefits only in terms of depression symptoms. The committee discussed that although this was limited evidence, behavioural couples therapy was included in the range of interventions offered by the IAPT services and that it was useful in the specific population and so recommended its use for this group of people.

Based on their overall review of the clinical evidence the committee agreed that some treatments (such as individual CBT, individual behavioural therapies, antidepressants and combinations of CBT, acupuncture and light therapy with antidepressants) appeared to be more effective than others in ranking, but there was otherwise little to choose between treatments. The committee therefore reviewed the results of the health economic modelling (see separate details of this discussion below) which determined which treatments were cost-effective, and used this to help refine a suggested prioritisation of which treatments should be offered to people with depression, or considered for use.

The committee discussed the fact that acupuncture in combination with antidepressants had been shown to be effective for some outcomes, but noted that the studies had been conducted in China using Chinese acupuncture techniques which were different to Western acupuncture techniques. They therefore agreed that the evidence may not be applicable to the UK population and that acupuncture plus antidepressants should not be recommended, and instead they made a research recommendation.

The committee considered the short-term and long-term harms associated with antidepressants, for example, side effects associated with SSRIs include drowsiness, nausea, insomnia, agitation, restlessness and sexual problems. For the TCAs there is the potential for cardiotoxicity and associated increased risk in overdose, although this is much greater for some TCAs such as amitriptyline and dosulepin. Some antidepressants, including the SNRIs venlafaxine and duloxetine, are also associated with more withdrawal symptoms. On the basis of the safety and tolerability profiles the committee agreed that SSRIs should be considered as the first choice of antidepressant for most people. SNRIs and TCAs were also

an option for the treatment of more severe depression, if indicated based on previous clinical and treatment history, although the guideline highlights that TCAs are dangerous in overdose and that of the TCAs lofepramine has the best safety profile. In developing the recommendations, the committee were mindful of the negative consequences of prolonged depressive episodes including not only the impact on the mental health of the individual and their family but also on an individual's physical health (depression is associated with poorer physical health outcomes) and the impact on employment. The committee agreed that the benefits of improving the outcome of a depressive episode outweighed the potential harms. However, the guideline included detailed recommendations about starting and stopping antidepressants, to enable people with depression and clinicians to make an individualised choice about the suitability of antidepressant treatment, and the choice of a specific antidepressant, based on patient preference and individual needs.

Cost effectiveness and resource use

According to existing UK economic evidence, computerised CBT with support was unlikely to be cost-effective compared with treatment as usual in adults with a new episode of more severe depression. Evidence was inconclusive regarding the cost effectiveness of non-directive counselling versus antidepressants. Sertraline was likely to be cost-effective compared with placebo and duloxetine, while escitalopram appeared to be more cost-effective than citalopram and duloxetine. Existing evidence also suggested that mirtazapine was more cost-effective than paroxetine; venlafaxine might be more cost-effective than fluoxetine and amitriptyline. Other evidence suggested that duloxetine was likely the most cost-effective option when compared with SSRIs, venlafaxine and mirtazapine. Finally, there was evidence that combination therapy (CBT and fluoxetine) was more cost-effective than pharmacological treatment (fluoxetine) alone; other available evidence suggested that CBT was likely to be more cost-effective than combination therapy (CBT and citalopram) and was inconclusive regarding the relative cost effectiveness between CBT and pharmacological therapy (citalopram).

Existing economic evaluations assessed a limited range of psychological interventions and no physical interventions; the range of comparisons made in each study was also limited. Moreover, there was inconsistency across some of the findings or inconclusiveness, so it was difficult for the committee to draw any robust conclusions on the relative cost effectiveness of the full range of interventions that are available for the treatment of adults with a new episode of more severe depression.

The guideline economic analysis assessed the cost effectiveness of a wide range of pharmacological, psychological, physical and combined interventions, as initial treatments for people with a new episode of more severe depression. The interventions included in the economic analysis were dictated by availability of data and were used as exemplars within their class regarding intervention costs as for practical reasons it was impossible to model all interventions considered in the guideline NMA. The committee noted that results of interventions could be extrapolated, with some caution, to other interventions of similar resource intensity within the same class.

Within each of the individual and group CT/CBT classes, there were two separate interventions of CBT≥15 sessions and CBT<15 sessions. Regarding individual CBT, CBT≥15 sessions appeared to have a somewhat smaller effect vs placebo compared with CBT<15 sessions (individual CBT≥15 sessions SMD -0.60, 95% CrI -0.90 to -0.30; individual CBT<15 sessions SMD -0.73, 95% CrI -1.08 to -0.41), but had a larger evidence base across RCTs on the SMD outcome (individual CBT≥15 sessions had N=626, whereas individual CBT<15 sessions had N=369). Individual CBT≥15 sessions was considered to have a more appropriate intensity for a population with more severe depression by the committee, it had also a wider evidence base than individual CBT<15 sessions, and given that individual CBT≥15 sessions and individual CBT<15 sessions had no very different effects versus placebo, individual CBT≥15 sessions was selected for consideration as an exemplar of its

class in the economic modelling (which ultimately informed guideline recommendations). Regarding group CBT, for the primary clinical outcome of SMD, there was only evidence on group CBT<15 sessions, therefore it was selected as the only intervention within its class in the economic modelling (which ultimately informed recommendations).

The economic analysis included only classes that had been tested on at least 50 participants across RCTs included in the NMAs of the SMD, discontinuation for any reason, response in completers and remission in completers, or fewer than 50 participants if the intervention class was one that was already in routine use in the NHS. To be considered in the economic analysis, treatment classes should have shown a better mean effect than the reference intervention, which was pill placebo. This was assumed in the model to reflect GP care. The NMAs of discontinuation (for any reason) and response in completers, which informed the economic analysis, were tested for the presence of bias due to small study size. Evidence of bias was identified in both analyses and therefore, in addition to the base-case economic analysis, a bias-adjusted economic analysis was run, using the outputs of the bias-adjusted NMAs on these two outcomes. The results of the bias-adjusted economic analysis were those considered by the committee when making recommendations.

The economic analysis utilised data on the risk of side effects from antidepressants obtained from a large US study that reported claims data. This risk ranged from 4.7% to 9.2%, depending on the antidepressant class. The committee selected these data because they expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, are more representative of the risk of side effects that have an impact on HRQoL and healthcare costs (which are of interest as they may have an impact on antidepressants' relative cost-effectiveness) compared with studies asking participants specifically to self-report the presence of side effects, or choose from a side-effect checklist. According to the committee's expert opinion, the latter study design tends to overestimate the prevalence of side effects. There was also a danger of the risk of side effects from antidepressants being overestimated in the economic model, since the risk of common side effects for psychological therapies was conservatively assumed to be zero. Nevertheless, the committee advised that a higher risk of side effects (40%) be tested in a sensitivity analysis. This had only a small impact on the cost-effectiveness and the ranking of antidepressants and the combination of individual CBT with antidepressants relative to other treatments.

The committee considered the bias-adjusted ranking of interventions for adults with a new episode of more severe depression, from the most to the least cost-effective. According to this ranking, individual problem-solving appeared to be the most cost-effective therapy, followed by the combination of individual CBT with antidepressants. Antidepressants (SSRIs, SNRIs, TCAs, mirtazapine and trazodone) also ranked highly, as did individual behavioural therapy, individual CBT, acupuncture with antidepressants, group exercise and cCBT with support. Other interventions, such as group CBT and non-directive counselling also appeared to be cost-effective compared with GP care. However, 5 interventions did not appear to be cost-effective compared with other cost-effective interventions and with GP care – these were cCBT without or with minimal support, interpersonal therapy, short-term psychodynamic psychotherapy (PDPT), individual exercise therapy and acupuncture.

The committee considered the 95% credible intervals (CrI) around the rankings of interventions and noted that these were characterised by considerable uncertainty. For example, the mean ranking of individual problem solving, which was shown to be the most cost-effective intervention, was 1.98, however its 95% CrI were 1 to 10, suggesting high uncertainty around the result for group CBT. For combined individual CBT and antidepressant, which was the second most cost-effective intervention, the mean ranking was 6.14 with 95% CrI ranging from 1 to 17. Similar uncertainty in the rankings was shown for all interventions included in the analysis. On the other hand, deterministic sensitivity analysis suggested that the results and the ranking of interventions were overall robust under different scenarios explored.

Based on the clinical and cost-effectiveness data, the committee decided to recommend individual CBT alone or combined with an antidepressant or individual behavioural therapies as the treatments of choice for a new episode of more severe depression in adults, as they had showed a beneficial effect compared to pill placebo, and were cost-effective classes in the economic analysis. The committee also recommended antidepressant medication as this had also been shown to be effective and cost-effective, even when using a higher risk of side effects in a sensitivity analysis. Although there was evidence of benefit for SSRIs, SNRIs, TCAs and mirtazapine the committee discussed that the tolerability of SSRIs and SNRIs meant that these would be considered as the preferred antidepressants. However, the committee agreed not to be too prescriptive about the choice of antidepressants as there may be people who had had a favourable response to TCAs in the past and would prefer to receive a TCA. Based on their knowledge and experience the committee added guidance on the safety concerns relating to overdose for TCAs, and advised that lofepramine has the best safety profile.. The committee discussed the role of mirtazapine for first-line treatment and agreed that its use should be reserved as a further-line option. The committee agreed that these treatment options should be discussed with people with depression and a shared decision made on which one was most appropriate for them based on their clinical needs and preferences.

The committee agreed that it was necessary to offer a choice of treatments, and that individual problem-solving and non-directive counselling had also been demonstrated to be cost-effective in more severe depression and so the committee recommended these as alternatives. The committee considered the fact that individual problem-solving was shown to be the most cost-effective treatment option in the economic analysis, but noted that relevant evidence was derived from US studies; problem solving is not available as a stand-alone intervention in the UK and, in some conceptualisations, it is only a variant of CBT, with very similar efficacy with individual CBT but higher uncertainty around the mean effect, as demonstrated by the NMA on the SMD outcome.

The committee noted that there was some evidence that group exercise and computerised CBT with support were both effective and cost-effective for more severe depression. However, the committee were uneasy about recommending these as interventions for more severe depression. This was based on their knowledge and experience, and concerns that these interventions may not be suitable for people with more severe depression as they did not require the development of a therapeutic relationship in the same way that the more intensive psychological therapies did, or that would occur when people were monitored regularly if on antidepressants. However, the committee agreed that as the evidence had shown benefit and cost-effectiveness these interventions could be considered for use in people with more severe depression who wished to try them, or who did not want to consider any other treatment options.

As described above, the committee decided not to recommend the combination of acupuncture with antidepressants because the evidence came from studies conducted in China using Chinese acupuncture techniques which were different to Western acupuncture techniques. They therefore agreed that the evidence may not be applicable to the UK population and instead they made a research recommendation.

The committee discussed the 5 interventions that appeared to be less cost-effective than GP care. They chose not to recommend individual exercise, as group exercise was included as a treatment option, as discussed above, and they did not recommend acupuncture, as acupuncture with SSRIs had been shown to be more effective and cost-effective and had not been recommended as an option. They chose not to recommend cCBT without or with minimal support as they had already recommended cCBT with support. However, the committee identified, based on their knowledge and experience, that there may be specific groups of people in whom STPP or IPT were effective and they therefore recommended these treatments be available as options for these specific groups.

The committee noted that long-term psychodynamic psychotherapy was included in the NMA for more severe depression, and had shown some evidence of effectiveness for the outcome of remission, but as no SMD data were available it was not possible to include it in the economic analysis and to fully consider its clinical effectiveness. Therefore, it was not possible to make any recommendations on this intervention.

The committee were concerned that psychological interventions are not always implemented consistently – for example audits have suggested that reduced numbers of sessions are used in practice compared with what is recommended, and that commissioners may not be clear how many sessions of a particular therapy are required. It was also important for people with depression to be aware of what was involved in the different types of therapy before making a decision. The committee therefore agreed it was important to specify the focus and structure of the psychological interventions being recommended to ensure consistency and that the services were commissioned correctly, and to highlight any particular advantages or drawbacks so that people could make an informed choice. The recommended structure of all psychological interventions (usual number of sessions) was based on the resource use utilised in the economic analysis, which, in turn, was informed by RCT resource use, modified by the committee's expert advice to represent optimal routine clinical practice in the UK. In this way, the recommended structure of psychological interventions represents cost-effective use of available healthcare resources as implemented in routine clinical practice. Nevertheless, the committee agreed that the recommended structure of psychological interventions should allow flexibility so that more sessions may be provided according to individual needs. The committee made no recommendation on the duration of sessions of psychological interventions, to allow flexibility in their delivery.

Other factors the committee took into account

In addition to the results of the network meta-analysis (NMA) the committee took other pragmatic factors into consideration when making recommendations, including the uncertainty and limitations around the clinical and cost-effectiveness data, and the need to provide a wide range of interventions to take into account individual needs and allow patient choice. The recommended first-line treatments for more severe depression were included in a table in the guideline in order to support shared decision-making. The treatment options are arranged in the suggested order in which they should be considered. However, the guideline recommends that all treatments in the table can be used as first-line treatments.

The committee discussed that the division of the population for this guideline into 'less severe' and 'more severe' using published cross-walk tables with an anchor score of 16 on the PHQ-9 scale, meant that the more severe population was people with moderate to severe depression and hence a wide range of treatments should be available to allow choice of treatments, and so that treatments could be tailored to individuals and taking into account any previous history of depression and its severity. The committee also discussed that allowing choice from a range of treatments may lead to lower discontinuation rates than had been seen in clinical trials where patients were assigned to a treatment.

The committee were aware of 2 studies that had been published after the cut-off date for inclusion in the evidence review for this guideline, although it was likely that neither would have met the inclusion criteria according to the protocol. However, the committee considered that these were important publications. The first of these was Barkham 2021 which was a pragmatic, randomised non-inferiority trial comparing counselling for depression (in this study called 'person-centred experiential therapy', PCET) with cognitive behavioural therapy (CBT) in 510 participants. The primary outcome was depression symptomatology measured using the PHQ-9 score at 6 months, with the secondary outcome of PHQ-9 at 12 months. This study concluded that PCET is non-inferior to CBT at 6 months, but that PCET is inferior to CBT at 12 months. The committee noted that 58% of the participants in this study were already receiving antidepressant medication and as such the study would not have met the protocol criteria for first-line treatment of a new episode of depression. The committee

discussed that the PCET used in this study was not the same as non-directive counselling and therefore this study does not provide evidence for the effectiveness of non-directive counselling. However, the committee considered that this study showed that PCET or counselling for depression may be effective, at least in the shorter term, but that CBT may be more beneficial in the longer term and therefore should usually be offered to patients as a preferred option.

The second study was Cuijpers 2021 which was a network meta-analysis of psychotherapies for depression, including CBT, behavioural activation (BA), problem-solving, interpersonal psychotherapy, psychodynamic therapy, life-review therapy, third-wave therapies and non-directive support counselling. The primary outcome was treatment response, and other outcomes were remission and acceptability. This study found that all therapies had significant effects compared to care-as-usual and waiting list, and that the effects of the therapies did not differ significantly from each other, except for non-directive supportive counselling, which was less effective than all the other types of therapy. No differences were found between any of the interventions in terms of acceptability. The committee considered that this study also supported their recommendations made based on their systematic review of the evidence, that all psychological treatments will provide some benefit, so offering a wide choice of treatments is appropriate, but that counselling, although it may be the preferred option for some people with depression, may not provide the same level of treatment response.

The committee noted that their recommendations for exercise interventions would need to be modified if necessary to ensure that people with disabilities were still able to access this as a treatment option, and they highlighted this in their recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 and 1.7.1 and research recommendations in the NICE guideline.

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Additional references to methodological issues

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Appendices

Appendix A – Review protocol

Review protocol for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 33. Review protocol

Topic	First-line treatment for adults with depression
Review questions	RQ. 2.1 For adults with a new episode of less severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination? RQ. 2.2. For adults with a new episode of more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?
Objectives	To identify the most effective first-line interventions for the treatment of a new episode of depression
Population	• Adults receiving first-line treatment for a new episode of depression, as defined by a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by baseline depression scores on validated scales (and including those with subthreshold [just below threshold] depressive symptoms) If some, but not all, of a study's participants are eligible for the review, for instance, mixed anxiety and depression diagnoses, then we will include a study if at least 80% of its participants are eligible for this review. Baseline mean scores are used to classify study population severity according to less severe (RQ 2.1) or more severe (RQ 2.2) using the thresholds outlined below. These thresholds are derived using standardization of depression measurement crosswalk tables (Wahl 2014; Rush 2003; Carmody 2006; Uher 2008). An anchor point of 16 on the PHQ-9 was selected on the basis of alignment with the clinical judgement of the committee and eligibility criteria in published studies. If baseline mean scores are not available, severity will be classified according to the inclusion criteria of the study or the description given by the study authors (but only in cases where this is unambiguous, for example 'severe' or 'subthreshold' or 'mild'). Severity thresholds: **Scale** | **Threshold** HAMD (17-item, 21-item and 24-item) | 16

Topic	First-line treatment for adults with depression
	<table><tr><td>MADRS (10-item)</td><td>22</td></tr><tr><td>PHQ-9</td><td>16</td></tr><tr><td>BDI-I (21-item)</td><td>22</td></tr><tr><td>BDI-II (21-item)</td><td>30</td></tr><tr><td>CES-D (20-item)</td><td>36</td></tr><tr><td>QIDS (16-item)</td><td>12</td></tr><tr><td>HADS-D (7-item)</td><td>12</td></tr></table>
Exclude	• Trials of women with antenatal or postnatal depression • Trials of children and young people (mean age under 18 years) • Trials of people with learning disabilities • Trials of people with bipolar disorder • Trials of adults in contact with the criminal justice system (not solely as a result of being a witness or victim) • Trials where more than 20% of the population have psychotic symptoms • Trials where more than 20% of the population have a coexisting personality disorder • Trials where more than 20% of the population have chronic depression (chronic depression defined as depression for at least 2 years, or persistent subthreshold symptoms [dysthymia], or double depression [an acute episode of major depressive disorder superimposed on dysthymia]) • Trials of further-line treatment • Trials of people with Seasonal Affective Disorder (SAD) Trials that specifically recruit participants with a physical health condition in addition to depression (e.g. depression in people with diabetes)
Intervention	The following interventions will be included: **Psychological interventions**: • Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group) • Cognitive and cognitive behavioural therapies (including CBT individual or group [defined as under or over 15 sessions], problem solving, rational emotive behaviour therapy [REBT] and third-wave cognitive therapies individual or group) • Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) • Interpersonal psychotherapy • Psychodynamic psychotherapies (including individual or group-based short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) • Psychoeducational interventions (including psychoeducational group programmes)

Topic	First-line treatment for adults with depression
	• Self-help with or without support (including cognitive bibliotherapy with or without support, computerised CBT [CCBT] with or without support, computerised psychodynamic therapy with or without support) • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) The following interventions are more appropriate for subgroups of adults with depression and as such will be considered only in pairwise comparisons (and not included in the NMA): • Couple interventions, including behavioural couples therapy (for people with problems in the relationship with their partner) **Pharmacological interventions**: To be included, pharmacological interventions needed to be licensed in the UK and in routine clinical use for the first-line treatment of depression. SSRIs • Citalopram • Escitalopram • Paroxetine • Sertraline • Fluoxetine • TCAs • Amitriptyline • Clomipramine • Lofepramine • Nortriptyline • Note: To improve connectivity, imipramine will be included in the network (because it has been used as a control in many trials) however it will not be considered as part of the decision problem SNRIs • Venlafaxine • Duloxetine Other antidepressant drugs: • Mirtazapine

Topic	First-line treatment for adults with depression
	• Trazodone Note that if necessary for connectivity in the network specific drugs that are excluded and 'any antidepressant' or 'any SSRI' or 'any TCA' nodes will be added where they have been compared against a psychological or physical intervention and/or combined with a psychological or physical intervention but they will not be considered as part of the decision problem. **Physical interventions**: • Acupuncture • Exercise (including yoga) • Light therapy (for depression, not SAD) **Psychosocial interventions**: • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR])
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual (TAU) • Waitlist • No treatment • Placebo If a study compares 'intervention + TAU vs TAU alone' it will be recoded as 'intervention vs no treatment'
Outcomes	**Critical outcomes:** **Efficacy** • Depression symptomatology (mean endpoint score or change in depression score from baseline) • Remission (usually defined as a cut off on a depression scale), this will be analysed for those randomised and for completers • Response (usually defined as at least 50% improvement from the baseline score on a depression scale), this will be analysed for those randomised and for completers The following depression scales will be included in the following hierarchy: • MADRS • HAMD • QIDS

Topic	First-line treatment for adults with depression

	• PHQ
	• CGI (for dichotomous outcomes only)
	• CES-D
	• BDI
	• HADS-D (depression subscale)
	• HADS (full scale)
	
	Only one continuous scale will be used per study
	
	• For studies reporting response and/or remission, the scale used in the study to define cut-offs for response and/or remission will be used
	• If more than one definition is used, a hierarchy of scales will be adopted (hierarchy listed above)
	
	For studies not reporting dichotomous data, a hierarchy of scales (see above) will be adopted for continuous outcomes
	
	Acceptability/tolerability
	• Discontinuation due to side effects (for pharmacological trials)
	• Discontinuation due to any reason (including side effects)
	
	Important, but not critical, outcomes:
	• Quality of life
	  • Quality of life (as assessed with a validated scale, including the 12-item/36-item Short-Form Survey [SF-12/SF-36], 26-item short version of the World Health Organization Quality of Life assessment [WHOQOL-BREF], EuroQoL [EQ5D], Quality of Life Depression Scale [QLDS], Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q], Quality of Life Inventory [QoLI], and World Health Organization 5-item Well-Being Index [WHO-5])
	• Personal, social, and occupational functioning
	  • Global functioning (as assessed with a validated scale, including Global Assessment of Functioning [GAF], Global Assessment Scale [GAS], and Social and Occupational Functioning Assessment Scale [SOFAS])
	  • Functional impairment (as assessed with a validated scale, including Sheehan Disability Scale [SDS], Social Adjustment Scale [SAS], and Work and Social Adjustment Scale [WSAS])
	  • Sleeping difficulties (as assessed with a validated scale, including Insomnia Severity Index [ISI] and Pittsburgh Sleep Quality Index [PSQI])
	  • Employment (for instance, % unemployed)

Topic	First-line treatment for adults with depression
	• Interpersonal problems (as assessed with a validated scale, including Inventory of Interpersonal Problems [IIP]) • Outcomes will be assessed at endpoint and follow-up (data for all available follow-up periods of at least 1-month post-intervention will be extracted and will be grouped into categories for analysis, for instance, 1-3 months, 4-6 months, 7-9 months, 10-12 months, 13-18 months, 19-24 months, and >2 years).
Study design	• RCTs • Systematic reviews of RCTs
Include unpublished data?	Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted from elsewhere (for instance, from the previous guideline)
Restriction by date	All relevant studies from existing reviews from the 2009 guideline and from previous searches (pre-2016) will be carried forward. Studies published between 2016 and the date the searches are run will be sought.
Minimum sample size	N = 10 in each arm Studies with <50% completion data (drop out of >50%) will be excluded.
Study setting	Primary, secondary, tertiary and social care settings. Non-English-language papers will be excluded (unless data can be obtained from an existing review).
The review strategy	**Data Extraction (selection and coding)** Citations from each search will be downloaded into EndNote and duplicates removed. Titles and abstracts of identified studies will be screened by two reviewers for inclusion against criteria, until a good inter-rater reliability has been observed (percentage agreement =>90%). Initially 10% of references will be double-screened. If inter-rater agreement is good then the remaining references will be screened by one reviewer. All primary-level studies included after the first scan of citations will be acquired in full and re-evaluated for eligibility at the time they are being entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction will be double-coded. Discrepancies or difficulties with coding will be resolved through discussion between reviewers or the opinion of a third reviewer will be sought. **Data Analysis** Pairwise comparisons (meta-analyses using random-effects models) will be conducted to combine results from similar studies. An intention to treat (ITT) approach will be taken where possible. Network meta-analysis (NMA) in a Bayesian framework will also be used to synthesise the data for all eligible interventions which are connected in a network of RCT comparisons. Interventions with similar effects (as determined by the committee) will be grouped into classes and class effects models will be fitted [Dias 2018]. The relative effects of the interventions within each class will be assumed to be distributed around a common

Topic	First-line treatment for adults with depression
	class mean with a within-class variance, permitting the borrowing of strength across interventions within each class. Classes which do not have enough evidence to estimate within-class variability of effects (i.e., a class with just 1 or 2 interventions) will share within-class variability with similar classes (as determined by the committee) where the variance can be estimated. For example, the individual cognitive and CBT class may borrow the within-class variance from the individual behavioural therapies class. If no such similar class is identified, we will assume zero variance in classes with only 1 or 2 interventions. In addition, the attention placebo, no treatment and TAU classes will share a within-class variance. If an 'any antidepressant' class is required to connect otherwise disconnected/excluded drugs to the network (as described under Intervention topic), its within-class variance will be equal to the maximum of the SSRI and TCA within-class variances. The random class effects assumption will be assessed by comparing the fit of fixed and random class effects models, where the former assumes the intervention effects within each class are the same (i.e., no within-class variability of effects). Continuous outcomes (SMDs) will be combined with dichotomous data to estimate intervention effects, using the methods described in the Appendix. The NMA will probably be restricted to critical outcomes at endpoint due to the likelihood of a lack of connectivity in a follow-up data network or in a network for important (but not critical) outcomes. The consistency of direct and indirect evidence will be assessed by fitting and comparing the fit of the NMA and unrelated mean effects (UME) models, the latter of which is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast [Dias 2011]. Each data point's contribution to the posterior mean residual deviance for the NMA model will be plotted against that for the UME model, to visually assess if specific data points are contributing to inconsistency. If the UME suggests there is evidence of inconsistency, node-split models will be fitted to assist in identifying loops of evidence with inconsistency [Dias 2010]. Risk of bias will be assessed at the study level using the Cochrane risk of bias tool. This assessment includes: adequacy of randomisation (sufficient description of randomisation method, allocation concealment and any baseline difference between groups); blinding (of participants, intervention administrators and outcome assessors); attrition ('at risk of attrition bias' defined as a dropout of more than 20% and completer analysis used, or a difference of >20% between the groups); selective reporting bias (is the protocol registered, are all outcomes reported); other bias (for instance, conflict of interest in funding). Risk of bias will also be assessed at the outcome level using GRADE. For heterogeneity, outcomes will be downgraded once if I2>50%, twice if I2 >80%. For imprecision, outcomes will be downgraded using rules of thumb. If the 95% CI is imprecise i.e. crosses the line of no effect and the threshold for clinical benefit/harm, 0.8

Topic	First-line treatment for adults with depression
	or 1.25 (dichotomous) or -0.5 or 0.5 SMD (for continuous), the outcome will be downgraded. Outcomes will be downgraded one or two levels depending on how many lines it crosses. If the 95% CI is not imprecise, we will consider whether the criterion for Optimal Information Size is met (for dichotomous outcomes, 300 events; for continuous outcomes, 400 participants), if not we will downgrade one level.
Heterogeneity (sensitivity analysis and subgroups)	Where possible, the influence of the following subgroups will be considered: • Primary care compared to secondary care • Inpatient compared to outpatient settings • Older adults (60 years and older) compared to younger adults (younger than 60 years) • BME populations • Men If the network structure allows, sensitivity analyses will be considered for depression symptoms (SMD, the primary outcome for the clinical analysis) and discontinuation for any reason and response in completers (the main outcomes for economic analysis), as follows: • Risk of bias as reflected by publication bias and study size using methods described in [Dias 2010]. We will assume possible bias in comparisons of active interventions vs inactive control and no bias between inactive control comparisons, as well as active intervention comparisons, except in comparisons where counselling is the control intervention (in which case bias against counselling will be assumed) • Validity of transitivity assumption will be explored by sensitivity analysis on SMD outcome that includes non-pharmacological trials only and examines any differences in magnitude of effects and ranking of non-pharmacological interventions compared to results from the mixed psychological, psychosocial, pharmacological and physical model Threshold analysis will be performed to assess the robustness of intervention recommendations due to bias [Phillippo 2018].
Notes	For interventions in the NMA it is assumed that any patient that meets all inclusion criteria is, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set. For defining routine usage of drugs, the national prescription cost data for England in 2017 - the most recent year for which relevant data existed - (Prescribing & Medicines Team, Health and Social Care Information Centre, 2017) was used. If a drug appeared in the top 15 it was included, with the exception of dosulepin which the BNF indicates should be initiated by a specialist. Cipriani 2018 network meta-analysis will be used as a source for studies and data. References for crosswalk tables:

Topic	First-line treatment for adults with depression
	Carmody, T. J., Rush, A. J., Bernstein, I., Warden, D., Brannan, S., Burnham, D., ... & Trivedi, M. H. (2006). The Montgomery Äsberg and the Hamilton ratings of depression: a comparison of measures. European Neuropsychopharmacology, 16(8), 601-611. Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., ... & Thase, M. E. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biological psychiatry, 54(5), 573-583. Uher, R., Farmer, A., Maier, W., Rietschel, M., Hauser, J., Marusic, A., ... & Henigsberg, N. (2008). Measuring depression: comparison and integration of three scales in the GENDEP study. Psychological medicine, 38(2), 289-300. Wahl, I., Löwe, B., Bjorner, J. B., Fischer, F., Langs, G., Voderholzer, U., ... & Rose, M. (2014). Standardization of depression measurement: a common metric was developed for 11 self-report depression measures. Journal of clinical epidemiology, 67(1), 73-86. Assuming a normal distribution and using baseline mean and standard deviation data, we will explore the categorisation of less and more severe, including the percentage of studies 'definitely' within the correct category (≥70% of the study sample above cut-off) in order to aid the committee in interpreting the results. References for data analysis: Dias, S., Ades, A.E., Welton, N.J., Jansen, J.P., Sutton, A.J. (2018). Network meta-analysis for decision making. Hoboken, NJ: Wiley. Dias, S., Welton, N.J., Sutton, A.J., Caldwell, D.M., … & Ades, A.E. (2011). NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials. Dias, S., Welton, N.J., Caldwell, D.M., Ades A.E. (2010a). Checking consistency in mixed treatment comparison meta-analysis. Statistics in Medicine, 29(7-8), 932-44. References for heterogeneity: Dias, S., Welton, N.J., Marinho, V.C.C., Salanti, G., … & Ades A.E. (2010b). Estimation and adjustment of bias in randomised evidence by using mixed treatment comparison meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society), 173(3), 613-29.

Topic	First-line treatment for adults with depression
	Phillippo, D.M., Welton, N.J., Dias, S., Didelez, V., Ades A.E. (2018). Sensitivity of treatment recommendations to bias in network meta-analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society), 181(3), 843-67.
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Cochrane Library; WEB OF SCIENCE
Identify if an update	Update of CG90 (2009)
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Navneet Kapur in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Topic	First-line treatment for adults with depression
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	CRD42019151328

BDI: Beck depression inventory; BME: black minority ethnic; BNF: British national formulary; (C)CBT: (computerised) cognitive behavioural therapy; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CES-D: Centre of epidemiology studies – depression; CGI: clinical global impressions; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; DSM: Diagnostic and statistical manual; EFT: emotion-focused therapy; EMDR: eye movement desensitization and reprocessing; EQ-5D: European quality of life 5 dimensions; GAF: global assessment of functioning; GAS: global assessment scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HADS-D: hospital anxiety and depression scale – depression; HAMD: Hamilton Depression Rating Scale; ICD: International classification of diseases; IIP: inventory of interpersonal problems; ISI: insomnia severity index; ITT: intention to treat; MADRS: Montgomery–Åsberg Depression Rating Scale; MBSR: Mindfulness-based stress reduction; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PHQ-9: patient health questionnaire-9; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QIDS: quick inventory of depressive symptomatology; QLDS: quality of life depression scale; Q-LES-Q: quality of life enjoyment and satisfaction questionnaire QOLI: quality of life inventory RCT: randomised controlled trial; REBT: rational emotive behaviour therapy; RoB: risk of bias; SAD: seasonal affective disorder; SAS: Spielberger state/trait anxiety scale; SDS: Sheehan disability scale; SMD: standardised mean difference; SNRI: serotonin-noradrenaline reuptake inhibitor; SOFAS: social and occupational functioning assessment scale; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant; UME: unrelated mean effects; WHOQOL-BRIEF: World health organization quality of life assessment (brief); WHO-5: world health organization 5-item wellbeing index; WSAS: work and social adjustment scale

Appendix B – Literature search strategies

Literature search strategies for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Clinical search

Database(s): Embase 1974 to 2019 Week 19, Emcare 1995 to present, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 14, 2019, PsycINFO 1806 to May Week 1 2019

Date of Search: 16/05/2019

Search updated: 04/06/2020

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/) use oemezd,emcr
2	(Depression/ or Depressive Disorder/ or Depressive Disorder, Major/ or Depressive Disorder, Treatment-Resistant/ or Disorders, Psychotic/ or Dysthymic Disorder/) use ppez
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/) use psyh
4	(depress* or dysthym* or melancholic* or ((affective or mood) adj disorder*)).tw.
5	((sever* or serious* or major* or chronic* or complex* or critical* or endur* or persist* or resist* or acute) adj2 (anxiety or (mental adj2 (disorder* or health or illness* or ill-health)) or (obsessive adj2 disorder*) or OCD or panic attack* or panic disorder* or phobi* or personality disorder* or psychiatric disorder* or psychiatric illness* or psychiatric ill-health*)).tw.
6	or/1-5
7	(exp psychotherapy/ or exp counseling/ or mindfulness/ or problem solving/ or psychiatric treatment/ or psychoeducation/ or self help/ or exp support group/) use oemezd,emcr
8	(exp Psychotherapy/ or Bibliotherapy/ or exp Cognitive Behavioral Therapy/ or exp Counseling/ or Problem Solving/ or Self Care/ or Self Efficacy/ or Self-Help Groups/) use ppez
9	(exp psychotherapy/ or behavioral activation system/ or bibliotherapy/ or cognitive therapy/ or exp counseling/ or group intervention/ or mindfulness/ or exp problem solving/ or psychoeducation/ or exp self-help techniques/ or support groups/) use psyh
10	((behavio* or abreact* or act* out* or age regression or assertive or autogenic or experiential) adj2 (activation or analys* or cathar* or condition* or intervention* or modification* or therap* or training or treatment*)).tw.
11	((cognitive adj2 (behavior* or therap*)) or (CBT* or CBASP or biofeedback or contingency management or covert conditioning or covert sensiti?ation or defusion or MBCT* or neurofeedback or problem focus* or problem solving or rational emotive or REBT or schema or solution focus*) or ((third wave or 3rd wave) adj2 (intervention* or therap* or treatment*))).tw.
12	(counsel* or ((art or creative or compassion* or conversation* or dialectic* or emotion* or group* or insight or narrative or non-directive or nondirective or non-specific or nonspecific or rational or client-centred or client-centered or humanistic or integrative or interpersonal or person-centred or person-centered or personal construct or persuasion or Rogerian or talking or time-limited) adj2 (intervention* or therap* or training or treatment*))).tw.
13	(psychotherap* or (psycho* adj (aid* or help* or intervention* or support* or therap* or training or treatment*)) or (balint group or group program* or mindfulness* or mind training or role play* or support group*)).tw.
14	(self-help or bibliotherap* or meditat* or self-analy* or self-esteem or self-control or self-imag* or self-validat* or stress manag* or (computer* adj2 (intervention* or program* or therap* or treatment*)) or CCBT).tw.
15	or/7-14
16	drug therapy/ or drug therapy.fs.
17	psychopharmacotherapy/ use oemezd,emcr,psyh
18	antidepressant agent/ use oemezd,emcr
19	Antidepressive Agents/ use ppez
20	antidepressant drugs/ use psyh
21	serotonin uptake inhibitor/ use oemezd,emcr
22	Serotonin Uptake Inhibitors/ use ppez
23	serotonin reuptake inhibitors/ use psyh
24	serotonin noradrenalin reuptake inhibitor/ use oemezd,emcr
25	"Serotonin and Noradrenaline Reuptake Inhibitors"/ use ppez
26	serotonin norepinephrine reuptake inhibitors/ use psyh
27	tricyclic antidepressant agent/ use oemezd,emcr
28	Antidepressive Agents, Tricyclic/ use ppez
29	tricyclic antidepressant drugs/ use psyh
30	monoamine oxidase inhibitor/ use oemezd,emcr

#	Searches
31	monoamine oxidase inhibitors/ use ppez,psyh
32	tetracyclic antidepressive agent/ use oemezd,emcr
33	amfebutamone/ or amineptine/ or amitriptyline/ or bupropion/ or clomipramine/ or chlorimipramine/ or citalopram/ or desipramine/ or duloxetine/ or Duloxetine Hydrochloride/ or escitalopram/ or fluvoxamine/ or fluoxetine/ or imipramine/ or lofepramine/ or mianserin/ or mirtazapine/ or moclobemide/ or nefazadone/ or nortriptyline/ or paroxetine/ or phenelzine/ or sertraline/ or venlafaxine/ or Venlafaxine Hydrochloride/
34	(antidepress* or amfebutamone or amineptin* or amitr?ptylin* or bupropion or chlorimipramine or clomipramin* or citalopram or desipramin* or duloxetin* or escitalopram or fluvoxamin* or fluoxetin* or imipramin* or lofepramin* or mianserin or mirtazapin* or moclobemide or nefazadon* or nortriptylin* or paroxetin* or phenelzin* or psychopharmacologic* or psychopharmacotherap* or sertralin* or venlafaxin* or SNRI* or SSRI* or TCA* or TeCA* or tetracyclic or tricyclic or ((monoamine or serotonin) adj2 inhibitor*)).tw.
35	or/16-34
36	(anticonvulsive agent/ or anticonvulsant therapy/) use oemezd,emcr
37	Anticonvulsants/ use ppez
38	anticonvulsive drugs/ use psyh
39	lamotrigine/ or (lamotrigine or anticonvul* or anti-convul*).tw.
40	or/38-39
41	neuroleptic agent/ use oemezd,emcr
42	Antipsychotic Agents/ use ppez
43	neuroleptic drugs/ use psyh
44	amisulpride/ or aripiprazole/ or olanzapine/ or quetiapine/ or Quetiapine Fumarate/ or risperidone/ or ziprasidone/
45	(antipsychotic* or anti-psychotic* or amisulpride or aripiprazole or olanzapine or psychotropic* or quetiapine or risperidone or ziprasidone).tw.
46	or/41-45
47	anxiolytic agent/ use oemezd,emcr
48	Anti-Anxiety Agents/ use ppez
49	tranquilizing drugs/ use psyh
50	buspirone/
51	(anxiolytic* or antianxiet* or anti-anxiet* or tranquili* or buspirone).tw.
52	or/47-51
53	central stimulant agent/ use oemezd,emcr
54	Central Nervous System Stimulants/ use ppez
55	CNS stimulating drugs/ use psyh
56	methylphenidate/ or (methylphenidate or ritalin).tw.
57	or/53-56
58	lithium/ or lithium.tw.
59	omega 3 fatty acid/ use oemezd,emcr
60	Fatty Acids, Omega-3/ use ppez
61	fatty acids/ use psyh
62	(omega adj ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)).tw.
63	thyroid hormone/ use oemezd,emcr
64	Thyroid Hormones/ use ppez
65	exp thyroid hormones/ use psyh
66	(thyroid hormone* or calcitonin or dextrothyroxine or diiodotyrosine or monoiodotyrosine or thyronines or thyroxine).tw.
67	or/58-66
68	acupuncture/ or acupuncture.tw.
69	electroconvulsive therapy/ use oemezd,emcr,ppez
70	electroconvulsive shock therapy/ use psyh
71	(ECT or ((electroconvuls* or electro-convuls*) adj2 (therap* or treatment*)) or electroshock* or (shock adj (therap* or treatment*))).tw.
72	exp exercise/
73	(exp Exercise Therapy/ or Physical Exertion/ or exp Physical Fitness/ or Bicycling/ or exp Running/ or Swimming/ or Walking/) use ppez
74	(exp kinesiotherapy/ or exp physical activity/ or fitness/ or exp sport/) use oemezd,emcr
75	(exp physical fitness/ or exp sports/) use psyh
76	yoga/
77	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking).tw.
78	or/68-77
79	peer group/ or mentoring/
80	peer relations/ use psyh
81	friendship/
82	Friends/ use ppez
83	(befriend* or friend* or mentor* or peer group* or peer support or (communit* adj (navigat* or support*))).tw.
84	or/79-83
85	or/15,35,40,46,52,57,67,78,84
86	6 and 85
87	Letter/ use ppez
88	letter.pt. or letter/ use oemezd,emcr
89	note.pt.
90	editorial.pt.

#	Searches
91	Editorial/ use ppez
92	News/ use ppez
93	exp Historical Article/ use ppez
94	Anecdotes as Topic/ use ppez
95	Comment/ use ppez
96	Case Report/
97	case study/ use oemezd,emcr
98	(letter or comment*).ti.
99	or/87-98
100	randomized controlled trial/
101	random*.ti,ab.
102	100 or 101
103	99 not 102
104	(animals/ not humans/) use ppez
105	(animal/ not human/) use oemezd,emcr
106	nonhuman/ use oemezd,emcr
107	exp animals/ use psyh
108	"primates (nonhuman)"/ use psyh
109	exp Animals, Laboratory/ use ppez
110	exp Animal Experimentation/ use ppez
111	exp animal experiment/ use oemezd,emcr
112	exp experimental animal/ use oemezd,emcr
113	exp Models, Animal/ use ppez
114	animal model/ use oemezd,emcr
115	animal models/ use psyh
116	animal research/ use psyh
117	exp Rodentia/ use ppez
118	exp rodent/ use oemezd,emcr
119	exp rodents/ use psyh
120	(rat or rats or mouse or mice).ti.
121	or/103-120
122	86 not 121
123	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
124	123 use ppez
125	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
126	125 use ppez
127	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
128	127 use oemezd,emcr
129	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
130	129 use psyh
131	124 or 126
132	128 or 130 or 131
133	Meta-Analysis/
134	exp Meta-Analysis as Topic/
135	systematic review/
136	meta-analysis/
137	(meta analy* or metanaly* or metaanaly*).ti,ab.
138	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
139	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
140	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
141	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
142	(search* adj4 literature).ab.
143	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
144	cochrane.jw.
145	((pool* or combined) adj2 (data or trials or studies or results)).ab.
146	(or/133-135,137,139-144) use ppez
147	(or/135-138,140-145) use oemezd,emcr
148	(or/133,137,139-144) use psyh
149	or/146-148
150	network meta-analysis/
151	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
152	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
153	or/150-152
154	or/132,149,153
155	122 and 154
156	limit 155 to english language

#	Searches
157	limit 156 to yr="2016 -Current"

The Cochrane Library, issue 5 of 12, May 2019

Date of search: 21/05/2019

Search updated: 04/06/2020

ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] this term only
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#6	MeSH descriptor: [Dysthymic Disorder] this term only
#7	(depress* or dysphori* or dysthym* or melanchol* or ((affective or mood) next disorder*)):ti,ab
#8	((sever* or serious* or major* or acute or chronic* or complex* or endur* or persist* or resist*) next/2 anxiety or (mental next/2 (disorder* or health or illness* or ill-health)) or (obsessive next/2 disorder*) or OCD or "panic attack*" or "panic disorder*" or phobi* or "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric ill-health*"):ti,ab
#9	{or #1-#8}
#10	MeSH descriptor: [Psychotherapy] explode all trees
#11	MeSH descriptor: [Bibliotherapy] this term only
#12	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
#13	MeSH descriptor: [Counseling] explode all trees
#14	MeSH descriptor: [Problem Solving] this term only
#15	MeSH descriptor: [Self Care] this term only
#16	MeSH descriptor: [Self Efficacy] this term only
#17	MeSH descriptor: [Self-Help Groups] this term only
#18	((behaviour* or behavior* or abreact* or "act* out*" or "age regression" or assertive or autogenic or experiential) next/2 (activation or analys* or cathar* or condition* or intervention* or modification* or therap* or training or treatment*)):ti,ab
#19	((cognitive next/2 (behavio* or therap*)) or (CBT* or CBASP or biofeedback or "contingency management" or "covert conditioning" or "covert sensitisation" or "covert sensiitization" or defusion or MBCT* or neurofeedback or "problem focus*" or "problem solving" or "rational emotive" or REBT or schema or "solution focus*") or (("third wave" or "3rd wave") next (intervention* or therap* or treatment*))):ti,ab
#20	(counsel* or ((art or creative or compassion* or conversation* or dialectic* or emotion* or group* or insight or narrative or non-directive or nondirective or non-specific or nonspecific or rational or client-centred or client-centered or humanistic or integrative or interpersonal or person-centred or person-centered or "personal construct*" or persuasion or Rogerian or talking or time-limited) next (intervention* or therap* or training or treatment*))):ti,ab
#21	(psychotherap* or (psycho* next (aid* or help* or intervention* or support* or therap* or training or treatment*)) or ("balint group*" or "group program*" or mindfulness* or "mind training" or "role play*" or "support group*")):ti,ab
#22	(self-help or bibliotherap* or meditat* or self-analy* or self-esteem or self-control or self-imag* or self-validat* or "stress manag*" or (computer* next/2 (intervention* or program* or therap* or treatment*)) or CCBT):ti,ab
#23	MeSH descriptor: [Drug Therapy] this term only
#24	MeSH descriptor: [Antidepressive Agents] this term only
#25	MeSH descriptor: [Serotonin Uptake Inhibitors] this term only
#26	MeSH descriptor: [Serotonin and Noradrenaline Reuptake Inhibitors] this term only
#27	MeSH descriptor: [Antidepressive Agents, Tricyclic] this term only
#28	MeSH descriptor: [Monoamine Oxidase Inhibitors] this term only
#29	MeSH descriptor: [Bupropion] this term only
#30	MeSH descriptor: [Amitriptyline] this term only
#31	MeSH descriptor: [Bupropion] this term only
#32	MeSH descriptor: [Clomipramine] this term only
#33	MeSH descriptor: [Clomipramine] this term only
#34	MeSH descriptor: [Citalopram] this term only
#35	MeSH descriptor: [Desipramine] this term only
#36	MeSH descriptor: [Duloxetine Hydrochloride] this term only
#37	MeSH descriptor: [Citalopram] this term only
#38	MeSH descriptor: [Fluvoxamine] this term only
#39	MeSH descriptor: [Fluoxetine] this term only
#40	MeSH descriptor: [Imipramine] this term only
#41	MeSH descriptor: [Lofepramine] this term only
#42	MeSH descriptor: [Mianserin] this term only
#43	MeSH descriptor: [Mirtazapine] this term only
#44	MeSH descriptor: [Moclobemide] this term only
#45	MeSH descriptor: [Nortriptyline] this term only
#46	MeSH descriptor: [Paroxetine] this term only
#47	MeSH descriptor: [Phenelzine] explode all trees

ID	Search
#48	MeSH descriptor: [Sertraline] this term only
#49	MeSH descriptor: [Venlafaxine Hydrochloride] this term only
#50	(antidepress* or amfebutamone or amineptin* or amitriptylin* or amitryptylin* or bupropion or chlorimipramine or clomipramin* or citalopram or desipramin* or duloxetin* or escitalopram or fluvoxamin* or fluoxetin* or imipramin* or lofepramin* or mianserin or mirtazapin* or moclobemide or nefazadon* or nortriptylin* or paroxetin* or phenelzin* or psychopharmacologic* or psychopharmacotherap* or sertralin* or venlafaxin* or SNRI* or SSRI* or TCA* or TeCA* or tetracyclic or tricyclic or ((monoamine or serotonin) next/2 inhibitor*)):ti,ab
#51	MeSH descriptor: [Anticonvulsants] this term only
#52	MeSH descriptor: [Lamotrigine] this term only
#53	(lamotrigine or anticonvul* or anti-convul*):ti,ab
#54	MeSH descriptor: [Antipsychotic Agents] this term only
#55	MeSH descriptor: [Amisulpride] this term only
#56	MeSH descriptor: [Aripiprazole] this term only
#57	MeSH descriptor: [Olanzapine] this term only
#58	MeSH descriptor: [Quetiapine Fumarate] this term only
#59	MeSH descriptor: [Risperidone] this term only
#60	(antipsychotic* or anti-psychotic* or amisulpride or aripiprazole or olanzapine or psychotropic* or quetiapine or risperidone or ziprasidone):ti,ab
#61	MeSH descriptor: [Anti-Anxiety Agents] this term only
#62	MeSH descriptor: [Buspirone] this term only
#63	(anxiolytic* or antianxiet* or anti-anxiet* or tranquilis* or tranquiliz* or buspirone):ti,ab
#64	MeSH descriptor: [Central Nervous System Stimulants] this term only
#65	MeSH descriptor: [Methylphenidate] this term only
#66	(methylphenidate or ritalin):ti,ab
#67	MeSH descriptor: [Lithium] this term only
#68	lithium:ti,ab
#69	MeSH descriptor: [Fatty Acids, Omega-3] explode all trees
#70	(omega next/2 ("fatty acid*" or "polyunsaturated fatty acid*" or PUFA*)):ti,ab
#71	MeSH descriptor: [Thyroid Hormones] explode all trees
#72	("thyroid hormone*" or calcitonin or dextrothyroxine or diiodotyrosine or monoiodotyrosine or thyronines or thyroxine):ti,ab
#73	MeSH descriptor: [Acupuncture] this term only
#74	acupuncture:ti,ab
#75	MeSH descriptor: [Electroconvulsive Therapy] this term only
#76	(ECT or ((electroconvuls* or electro-convuls*) next/2 (therap* or treatment*)) or electroshock* or (shock next (therap* or treatment*))):ti,ab
#77	MeSH descriptor: [Exercise Therapy] explode all trees
#78	MeSH descriptor: [Physical Exertion] this term only
#79	MeSH descriptor: [Physical Fitness] explode all trees
#80	MeSH descriptor: [Bicycling] this term only
#81	MeSH descriptor: [Running] explode all trees
#82	MeSH descriptor: [Swimming] this term only
#83	MeSH descriptor: [Walking] this term only
#84	MeSH descriptor: [Yoga] this term only
#85	(exercis* or yoga or cycling or bicycling or jogging or running or sport* or swimming or walking):ti,ab
#86	MeSH descriptor: [Peer Group] this term only
#87	MeSH descriptor: [Mentoring] this term only
#88	MeSH descriptor: [Friends] this term only
#89	(befriend* or friend* or mentor* or "peer group*" or "peer support" or (communit* next (navigat* or support*))):ti,ab
#90	{or #10-#89}
#91	#9 and #90 with Cochrane Library publication date Between Jan 2016 and May 2019, in Cochrane Reviews, Cochrane Protocols, Trials

Health Economics search

Database(s): Embase 1974 to 2019 Week 08, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 26, 2019, PsycINFO 1806 to February Week 1 2019

Date of Search: 27/02/2019

Search updated: 02/03/2021

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysphoria/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or "mixed depression and dementia"/ or premenstrual dysphoric disorder/ or reactive depression/ or recurrent brief depression/ or seasonal affective disorder/ or treatment resistant depression/) use oemezd

#	Searches
2	((Depression/ or exp Depressive Disorder/ or Adjustment Disorders/ or Affective Disorders, Psychotic/ or Factitious Disorders/ or Premenstrual Dysphoric Disorder/) use ppez
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/ or premenstrual dysphoric disorder/ or seasonal affective disorder/) use psyh
4	(depress* or dysphori* or dysthym* or melanchol* or seasonal affective disorder* or ((affective or mood) adj disorder*)).tw.
5	or/1-4
6	Letter/ use ppez
7	letter.pt. or letter/ use oemezd
8	note.pt.
9	editorial.pt.
10	Editorial/ use ppez
11	News/ use ppez
12	exp Historical Article/ use ppez
13	Anecdotes as Topic/ use ppez
14	Comment/ use ppez
15	Case Report/
16	case study/ use oemezd
17	(letter or comment*).ti.
18	or/6-17
19	randomized controlled trial/
20	random*.ti,ab.
21	19 or 20
22	18 not 21
23	(animals/ not humans/) use ppez
24	(animal/ not human/) use oemezd
25	nonhuman/ use oemezd
26	exp animals/ use psyh
27	"primates (nonhuman)"/ use psyh
28	exp Animals, Laboratory/ use ppez
29	exp Animal Experimentation/ use ppez
30	exp animal experiment/ use oemezd
31	exp experimental animal/ use oemezd
32	exp Models, Animal/ use ppez
33	animal model/ use oemezd
34	animal models/ use psyh
35	animal research/ use psyh
36	exp Rodentia/ use ppez
37	exp rodent/ use oemezd
38	exp rodents/ use psyh
39	(rat or rats or mouse or mice).ti.
40	or/22-39
41	5 not 40
42	Economics/
43	Value of life/
44	exp "Costs and Cost Analysis"/
45	exp Economics, Hospital/
46	exp Economics, Medical/
47	Economics, Nursing/
48	Economics, Pharmaceutical/
49	exp "Fees and Charges"/
50	exp Budgets/
51	(or/42-50) use ppez
52	health economics/
53	exp economic evaluation/
54	exp health care cost/
55	exp fee/
56	budget/
57	funding/
58	(or/52-57) use oemezd
59	exp economics/
60	exp "costs and cost analysis"/
61	cost containment/
62	money/
63	resource allocation/
64	(or/59-63) use psyh
65	budget*.ti,ab.
66	cost*.ti.
67	(economic* or pharmaco?economic*).ti.
68	(price* or pricing*).ti,ab.

#	Searches
69	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
70	(financ* or fee or fees).ti,ab.
71	(value adj2 (money or monetary)).ti,ab.
72	or/65-70
73	51 or 58 or 64 or 72
74	Quality-Adjusted Life Years/ use ppez
75	Sickness Impact Profile/
76	quality adjusted life year/ use oemezd
77	"quality of life index"/ use oemezd
78	(quality adjusted or quality adjusted life year*).tw.
79	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
80	(illness state* or health state*).tw.
81	(hui or hui2 or hui3).tw.
82	(multiattibute* or multi attribute*).tw.
83	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
84	utilities.tw.
85	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
86	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
87	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
88	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
89	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
90	Quality of Life/ and ec.fs.
91	Quality of Life/ and (health adj3 status).tw.
92	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
93	(quality of life or qol).tw. and cost benefit analysis/ use oemezd
94	(quality of life or qol).tw. and "costs and cost analysis"/ use psyh
95	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
96	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
97	cost benefit analysis/ use oemezd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
98	"costs and cost analysis"/ use psyh and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
99	*quality of life/ and (quality of life or qol).ti.
100	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
101	quality of life/ and health-related quality of life.tw.
102	Models, Economic/ use ppez
103	economic model/ use oemezd
104	or/74-101
105	73 or 104
106	41 and 105
107	limit 106 to english language
108	limit 107 to yr="2016 -Current"

Database(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA)

Searched: 26/02/2019

#	Searches
#1	MESH DESCRIPTOR: depressive disorder EXPLODE ALL TREES
#2	((depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder* or affective disorder* or mood disorder*))
#3	#1 or #2 IN HTA FROM 2016 TO 2019

Database(s): CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature) 1937-current, EBSCO Host

Date of search: 26/02/2019

Search updated: 02/03/2021

#	Query	Limiters/Expanders
S31	S4 AND S30	Limiters - Publication Year: 2016-2019; Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase

#	Query	Limiters/Expanders
S30	S10 OR S29	Search modes - Boolean/Phrase
S29	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S28	(MH "Quality of Life") AND TX (health-related quality of life)	Search modes - Boolean/Phrase
S27	(MH "Quality of Life") AND TI (quality of life or qol)	Search modes - Boolean/Phrase
S26	AB ((qol or hrqol or quality of life) AND ((qol or hrqol* or quality of life) N2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)))	Search modes - Boolean/Phrase
S25	(MH "Cost Benefit Analysis") AND TX ((quality of life or qol) or (cost-effectiveness ratio* and (perspective* or life expectanc*))	Search modes - Boolean/Phrase
S24	(MH "Quality of Life") TX (health N3 status)	Search modes - Boolean/Phrase
S23	(MH "Quality of Life") AND TX ((quality of life or qol) N (score*1 or measure*1))	Search modes - Boolean/Phrase
S22	TX (time trade off*1 or time tradeoff*1 or tto or timetradeoff*1)	Search modes - Boolean/Phrase
S21	TX (sf36 or sf 36 or sf thirty six or sf thirtysix)	Search modes - Boolean/Phrase
S20	TX (euro* N3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*))	Search modes - Boolean/Phrase
S19	TX (eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol)	Search modes - Boolean/Phrase
S18	TI utilities	Search modes - Boolean/Phrase
S17	TX (utilit* N3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*))	Search modes - Boolean/Phrase
S16	TX (multiattibute* or multi attribute*)	Search modes - Boolean/Phrase
S15	TX (hui or hui2 or hui3)	Search modes - Boolean/Phrase
S14	TX (illness state* or health state*)	Search modes - Boolean/Phrase
S13	TX (quality adjusted or quality adjusted life year*or qaly* or qal or qald* or qale* or qtime* or qwb* or daly)	Search modes - Boolean/Phrase
S12	(MH "Sickness Impact Profile")	Search modes - Boolean/Phrase
S11	(MH "Quality-Adjusted Life Years")	Search modes - Boolean/Phrase
S10	S5 OR S6 OR S7 OR S8 OR S9	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S9	TX (value N2 (money or monetary))	Search modes - Boolean/Phrase
S8	TX (cost* N2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*))	Search modes - Boolean/Phrase
S7	TI cost* or economic* or pharmaco?economic*	Search modes - Boolean/Phrase
S6	TX budget* or fee or fees or finance* or price* or pricing	Search modes - Boolean/Phrase
S5	(MH "Fees and Charges+") OR (MH "Costs and Cost Analysis+") OR (MH "Economics") OR (MH "Economic Value of Life") OR (MH "Economics, Pharmaceutical") OR (MH "Economic Aspects of Illness") OR (MH "Resource Allocation+")	Search modes - Boolean/Phrase
S4	S1 OR S2 OR S3	Limiters - Exclude MEDLINE records; Language: English Search modes - Boolean/Phrase
S3	TX (depress* or dysphori* or dysthym* or melanchol* or seasonal affective disorder)	Search modes - Boolean/Phrase
S2	(MH "Adjustment Disorders+") OR (MH "Factitious Disorders") OR (MH "Affective Disorders, Psychotic")	Search modes - Boolean/Phrase
S1	(MH "Depression+") OR (MH "Premenstrual Dysphoric Disorder") OR (MH "Seasonal Affective Disorder")	Search modes - Boolean/Phrase

Additional EMDR search

Database(s): Embase 1980 to 2021 Week 43, Emcare 1995 to present, Ovid MEDLINE(R) ALL 1946 to November 03, 2021, APA PsycInfo 1806 to November Week 1 2021

Date of Search: 04/11/2021

#	Searches
1	(depression/ or agitated depression/ or atypical depression/ or depressive psychosis/ or dysthymia/ or endogenous depression/ or involutional depression/ or late life depression/ or major depression/ or masked depression/ or melancholia/ or "mixed anxiety and depression"/ or reactive depression/ or recurrent brief depression/ or treatment resistant depression/) use emez,emcr
2	(Depression/ or Depressive Disorder/ or Depressive Disorder, Major/ or Depressive Disorder, Treatment-Resistant/ or Disorders, Psychotic/ or Dysthymic Disorder/) use medall
3	("depression (emotion)"/ or exp major depression/ or affective disorders/ or atypical depression/) use psyh
4	(depress* or dysthym* or melanchol* or ((affective or mood) adj disorder*)).tw.

#	Searches
5	((sever* or serious* or major* or chronic* or complex* or critical* or endur* or persist* or resist* or acute) adj2 (anxiety or (mental adj2 (disorder* or health or illness* or ill-health)) or (obsessive adj2 disorder*) or OCD or panic attack* or panic disorder* or phobi* or personality disorder* or psychiatric disorder* or psychiatric illness* or psychiatric ill-health*)).tw.
6	or/1-5
7	(eye movement desensiti?ation or EMDR).tw.
8	6 and 7
9	Meta-Analysis/
10	exp Meta-Analysis as Topic/
11	systematic review/
12	meta-analysis/
13	(meta analy* or metanaly* or metaanaly*).ti,ab.
14	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
15	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
16	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
17	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
18	(search* adj4 literature).ab.
19	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
20	cochrane.jw.
21	((pool* or combined) adj2 (data or trials or studies or results)).ab.
22	(or/9-11,13,15-20) use medall
23	(or/11-14,16-21) use emez,emcr
24	(or/9,13,15-20) use psyh
25	or/22-24
26	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi?ed or randomly).ab. or trial.ti.
27	26 use medall
28	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi?ed or randomly or trial).ab.
29	28 use medall
30	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
31	30 use emez,emcr
32	clinical trials/ or (placebo or randomi?ed or randomly).ab. or trial.ti.
33	32 use psyh
34	27 or 29
35	31 or 33 or 34
36	network meta-analysis/
37	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
38	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
39	or/36-38
40	25 or 35 or 39
41	8 and 40
42	limit 41 to english language

The Cochrane Library, issue 10 of 12, October 2021

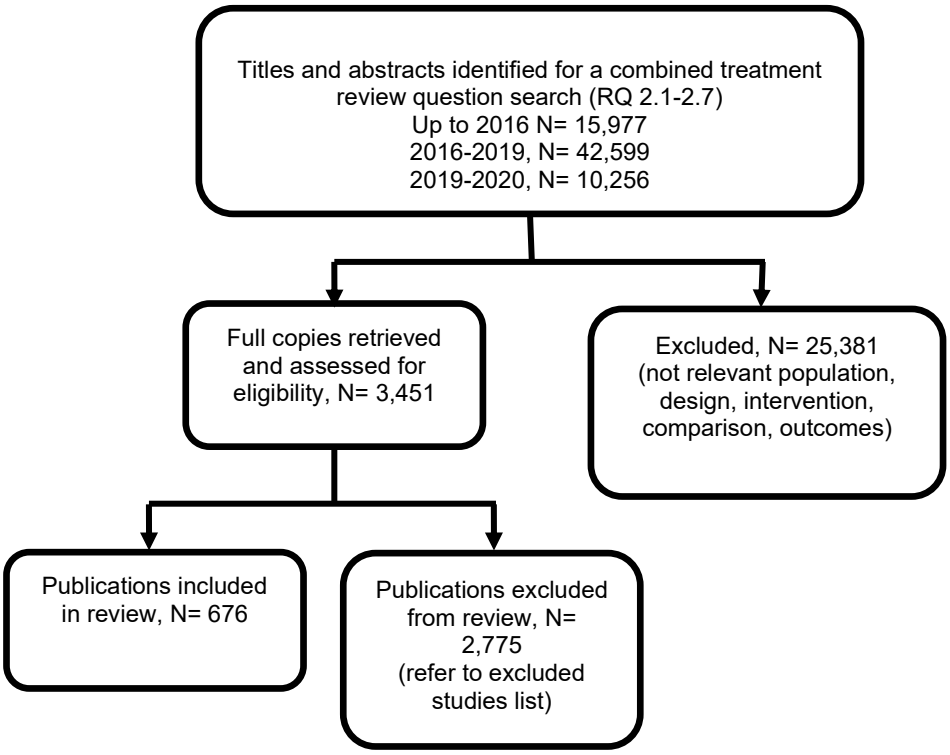
Date of search: 04/11/2021

ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] this term only
#3	MeSH descriptor: [Depressive Disorder, Major] this term only
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	MeSH descriptor: [Affective Disorders, Psychotic] this term only
#6	MeSH descriptor: [Dysthymic Disorder] this term only
#7	(depress* or dysphori* or dysthym* or melanchol* or ((affective or mood) next disorder*)):ti,ab
#8	((sever* or serious* or major* or acute or chronic* or complex* or endur* or persist* or resist*) next/2 anxiety or (mental next/2 (disorder* or health or illness* or "ill health")) or (obsessive next/2 disorder*) or OCD or "panic attack*" or "panic disorder*" or phobi* or "personality disorder*" or "psychiatric disorder*" or "psychiatric illness*" or "psychiatric ill-health*"):ti,ab
#9	{or #1-#8}
#10	("eye movement desensitisation" or "eye movement desensitization" or EMDR):ti,ab
#11	#9 and #10

Appendix C – Clinical evidence study selection

Study selection for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Figure 17: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence table for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Please refer to supplement B1 - Clinical evidence tables for treatment of a new episode of depression

Appendix E – Forest plots

Forest plots for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Please refer to supplements B2 and B3 for forest plots for studies included in the NMA treatment of a new episode of less severe depression and more severe depression, respectively

Forest plots for review questions: For adults with a new episode of less severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

This section includes forest plots only for outcomes that were synthesised using pairwise meta-analysis but were not included in the NMA (couple interventions) and sub-group analyses.

Subgroup analyses

Subgroup analyses of older adults (60 years and older) compared to younger adults (younger than 60 years)

Exercise individual versus waitlist

Figure 18: Depression symptoms endpoint

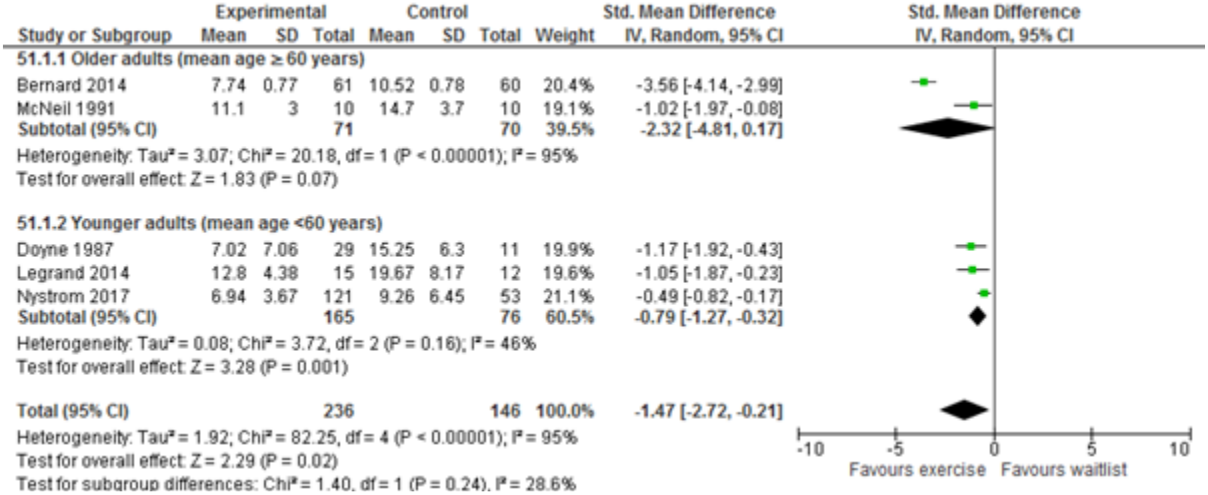


Figure 19: Depression symptoms change score

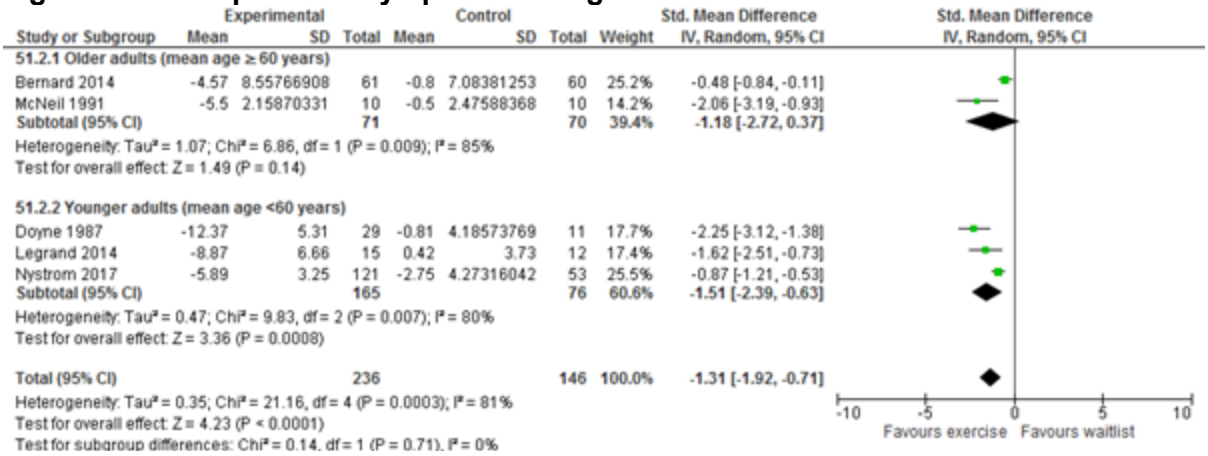
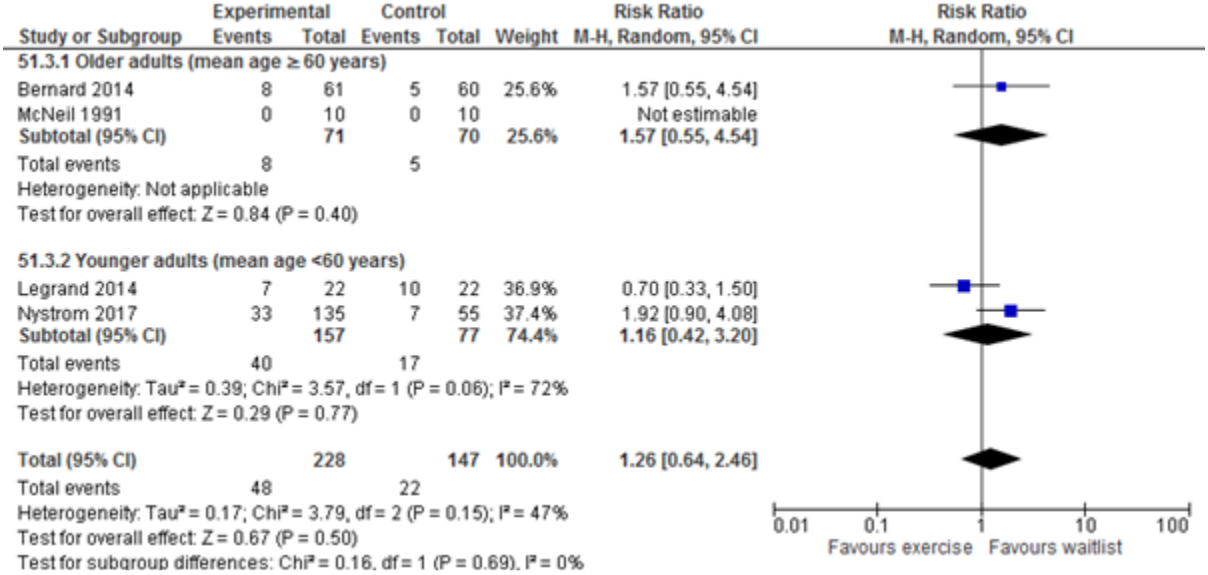


Figure 20: Discontinuation due to any reason



Forest plots for review question: For adults with a new episode of more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Subgroup analyses

Subgroup analyses of older adults (60 years and older) compared to younger adults (younger than 60 years)

SSRIs versus placebo

Figure 21: Depression symptoms endpoint

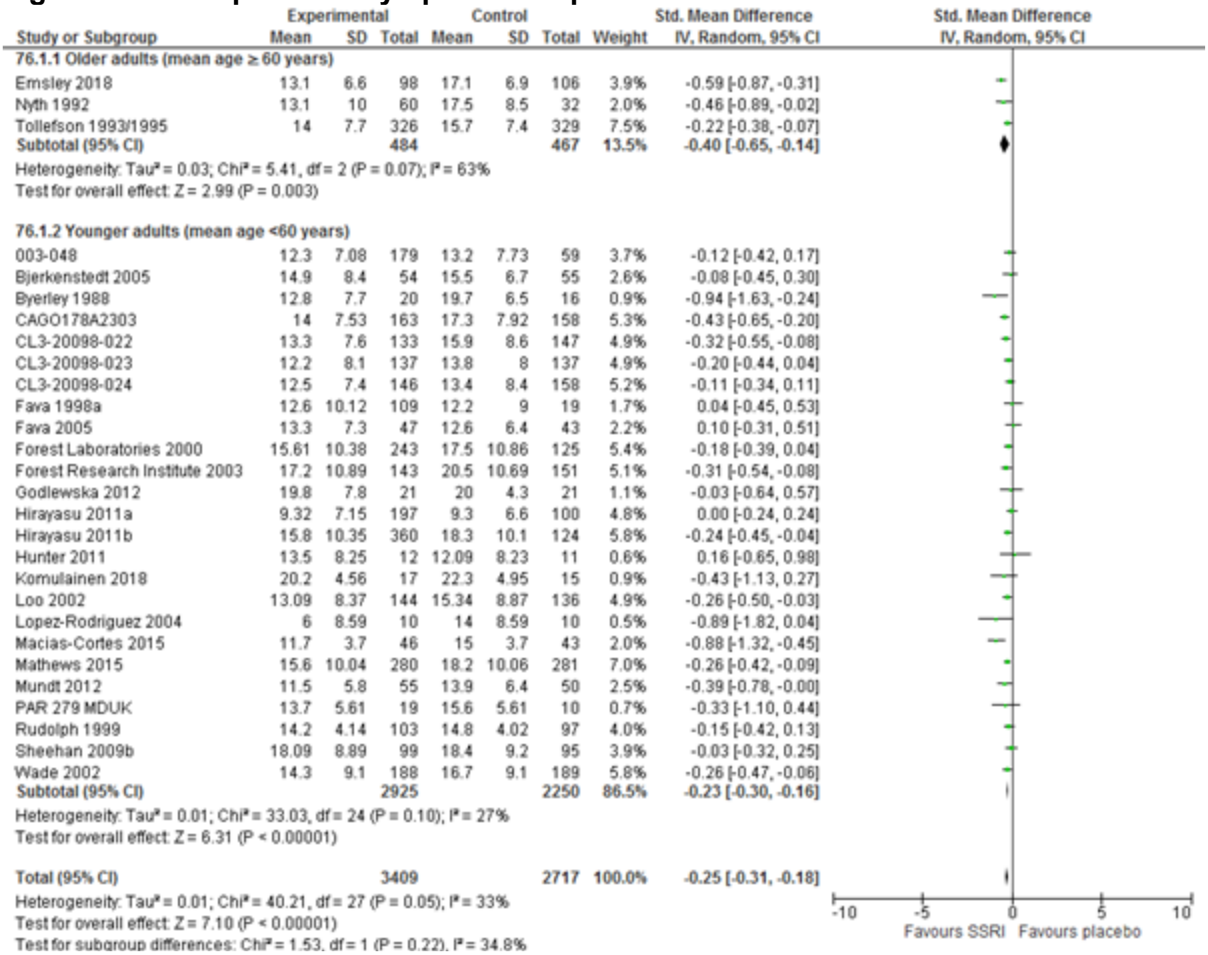


Figure 22: Depression symptoms change score

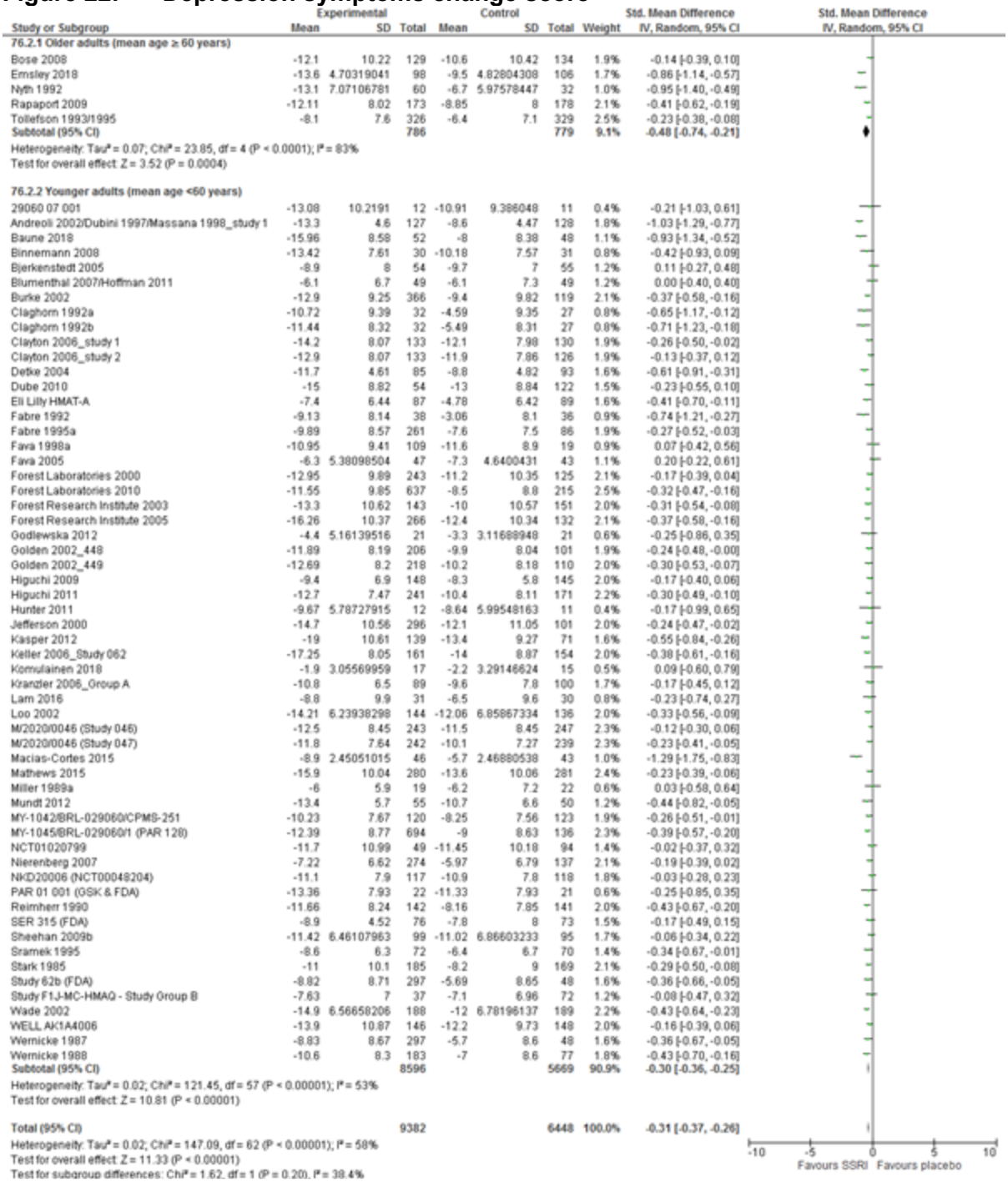


Figure 23: Remission

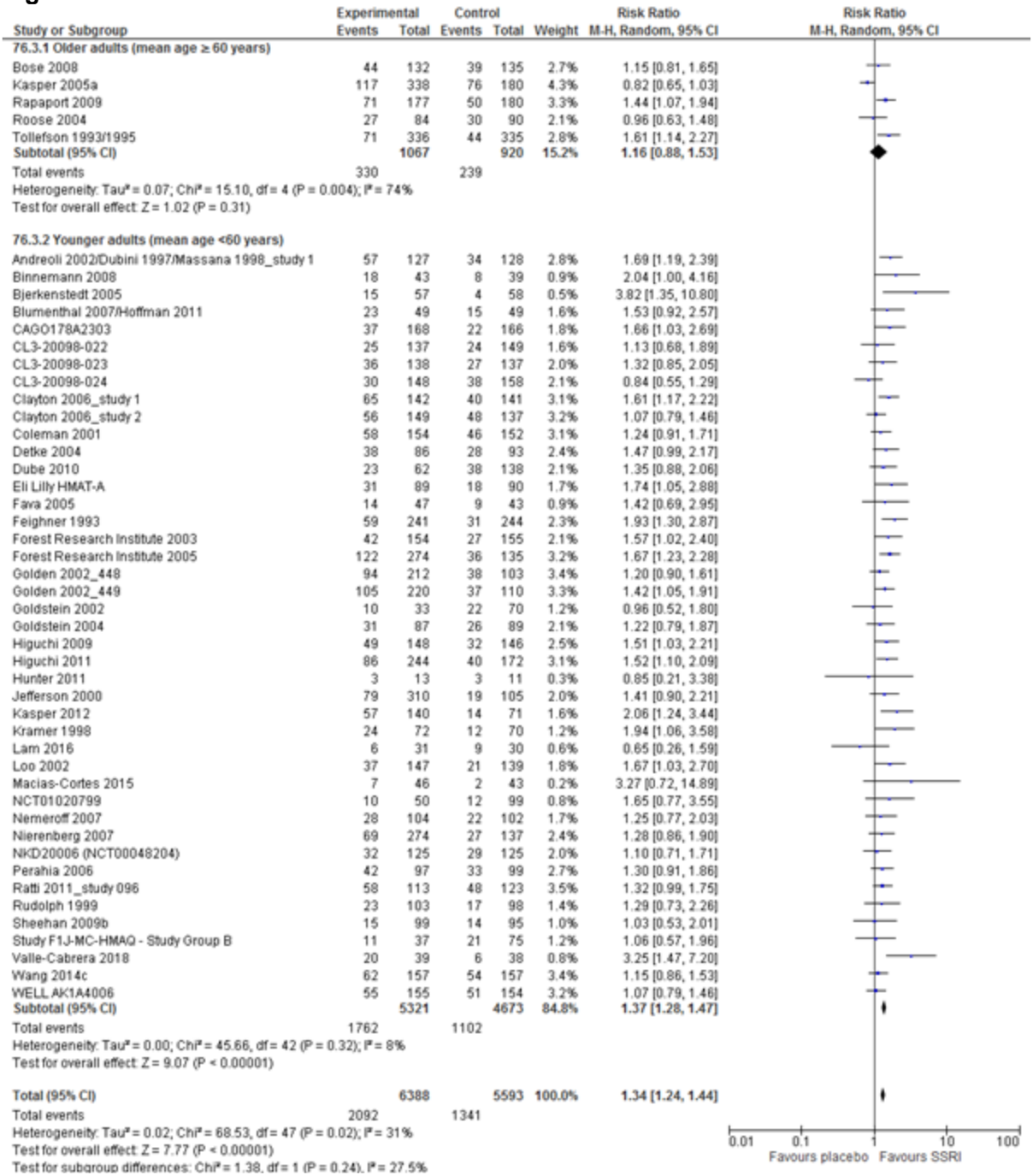


Figure 24: Response

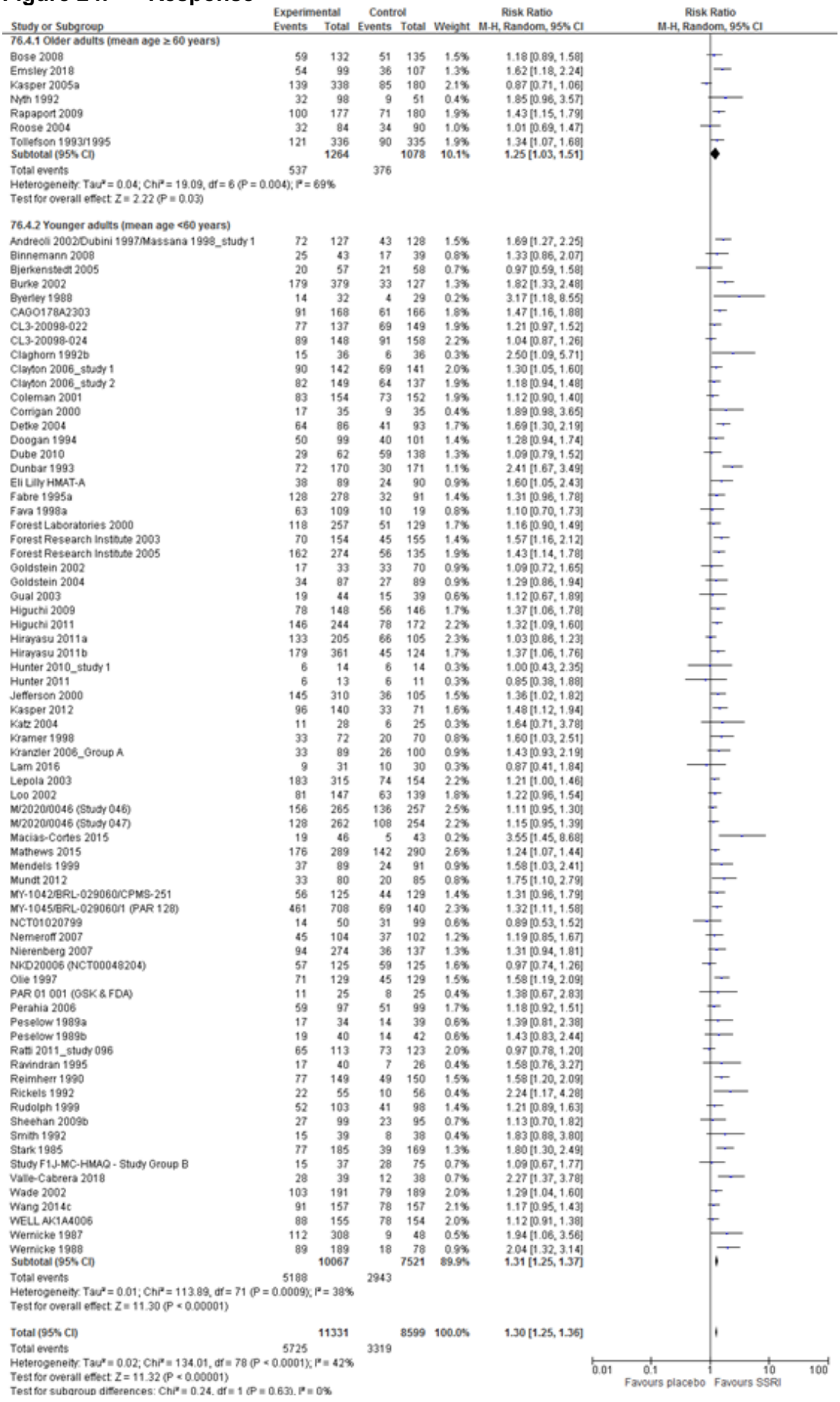


Figure 25: Discontinuation due to side effects

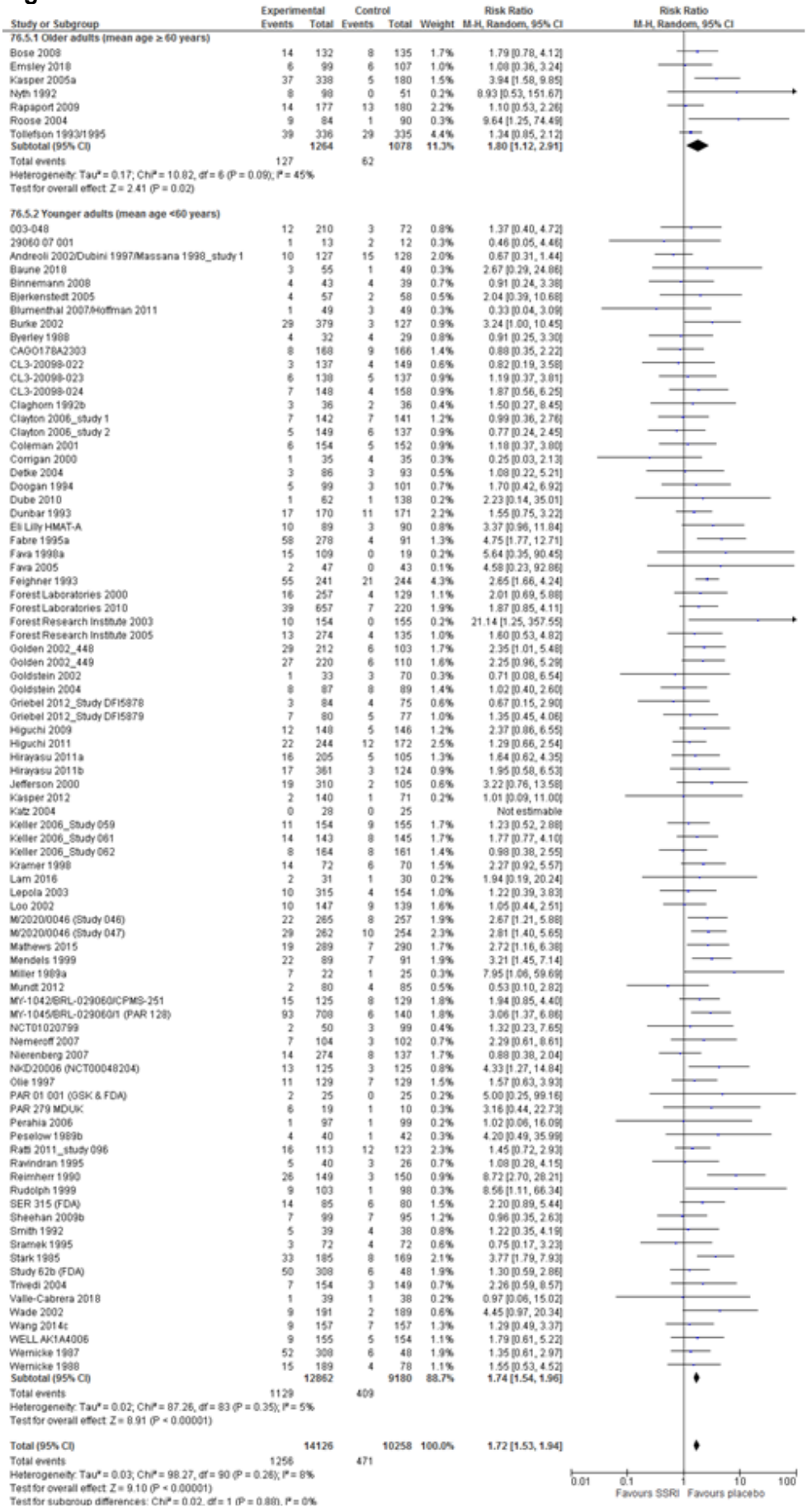
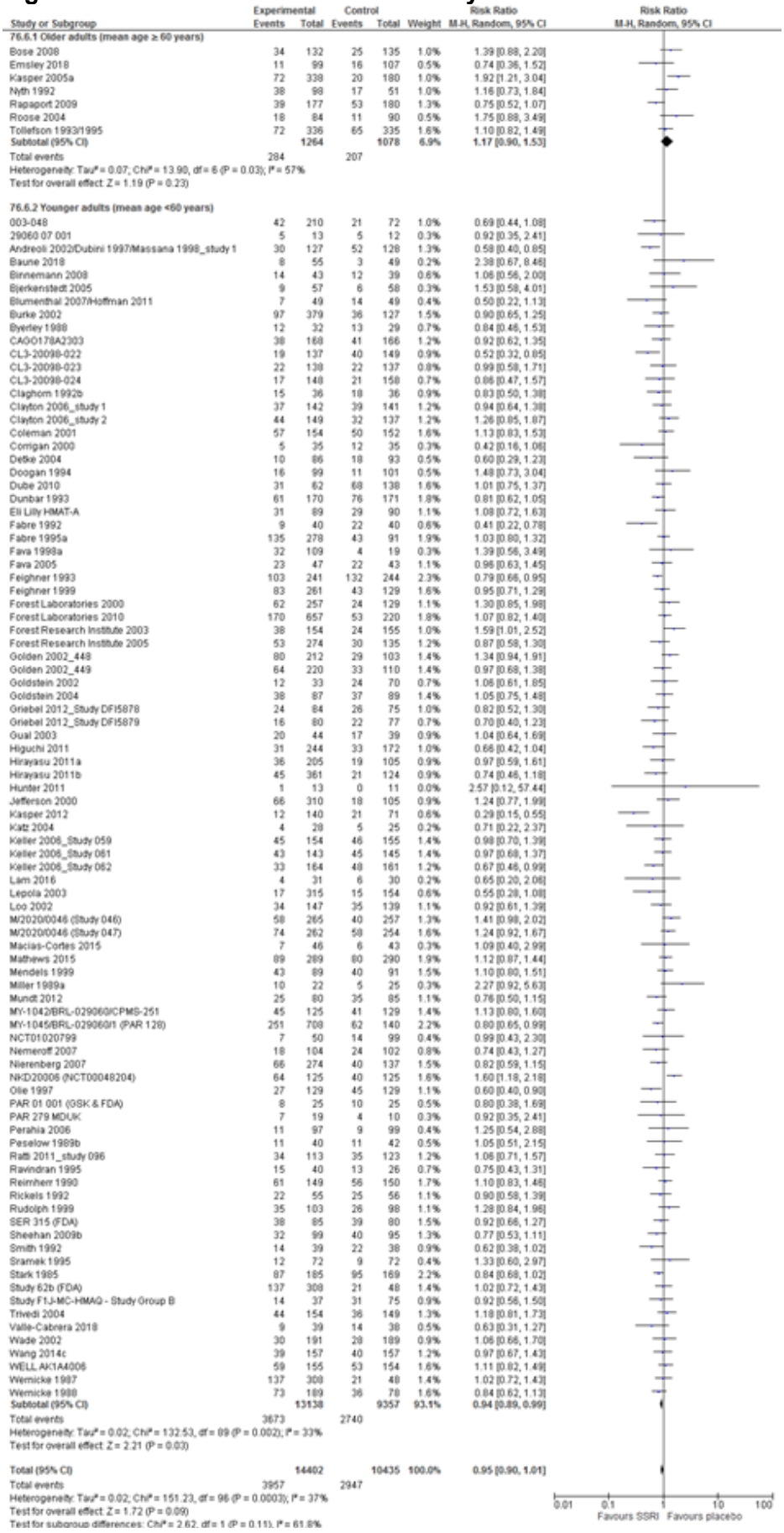


Figure 26: Discontinuation due to any reason



SSRIs versus TCAs

Figure 27: Depression symptoms endpoint

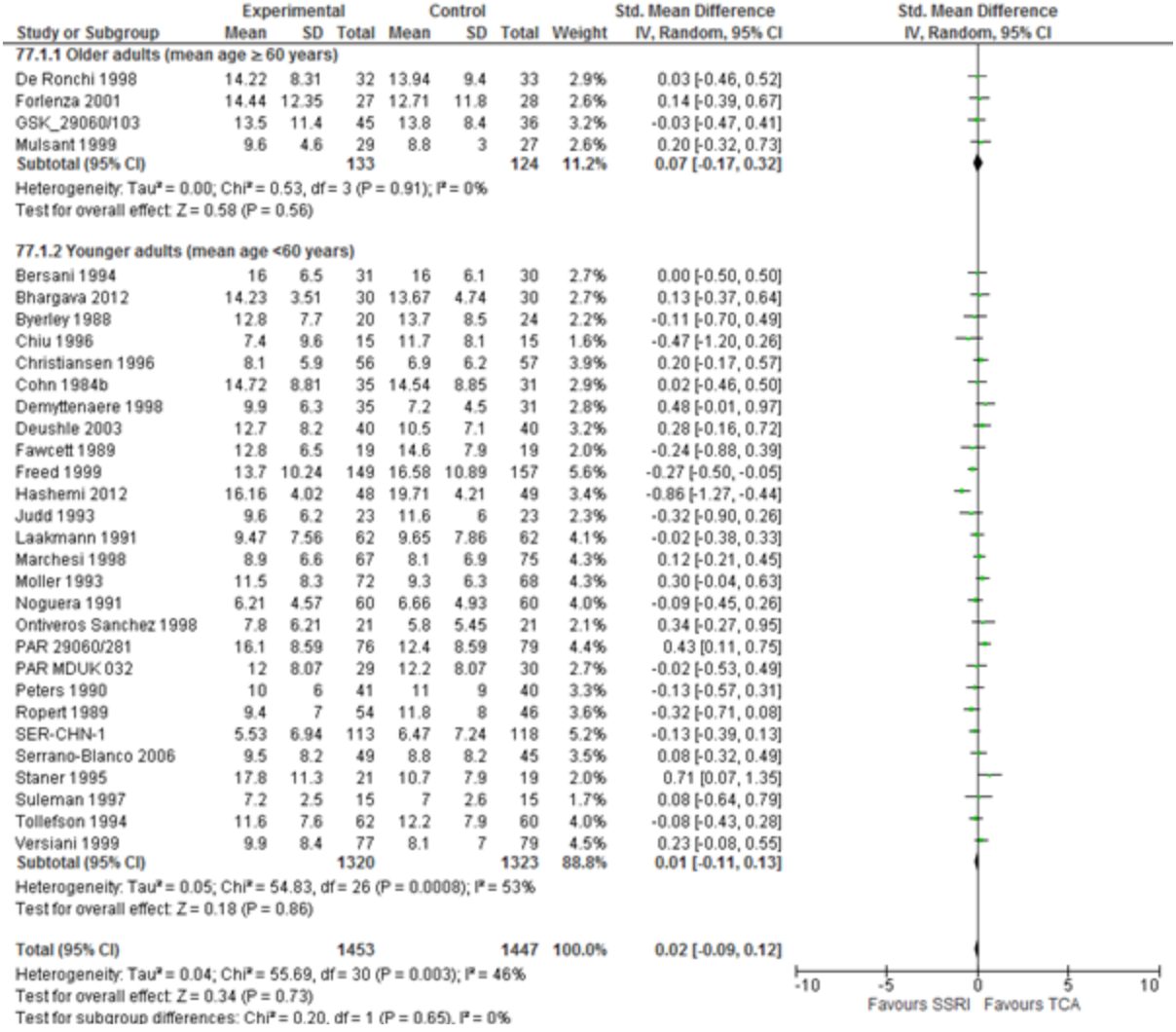


Figure 28: Depression symtoms change score

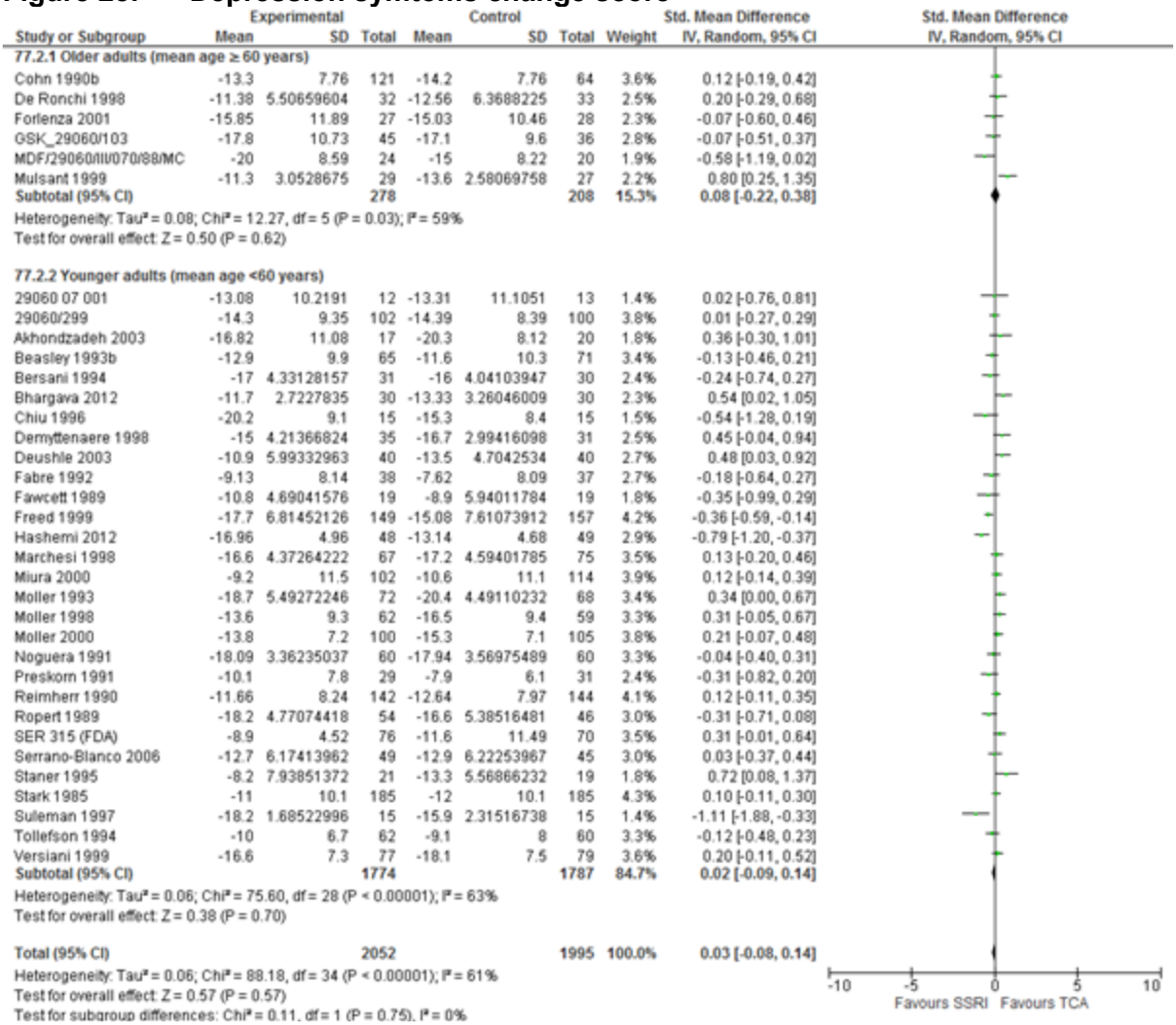


Figure 29: Remission

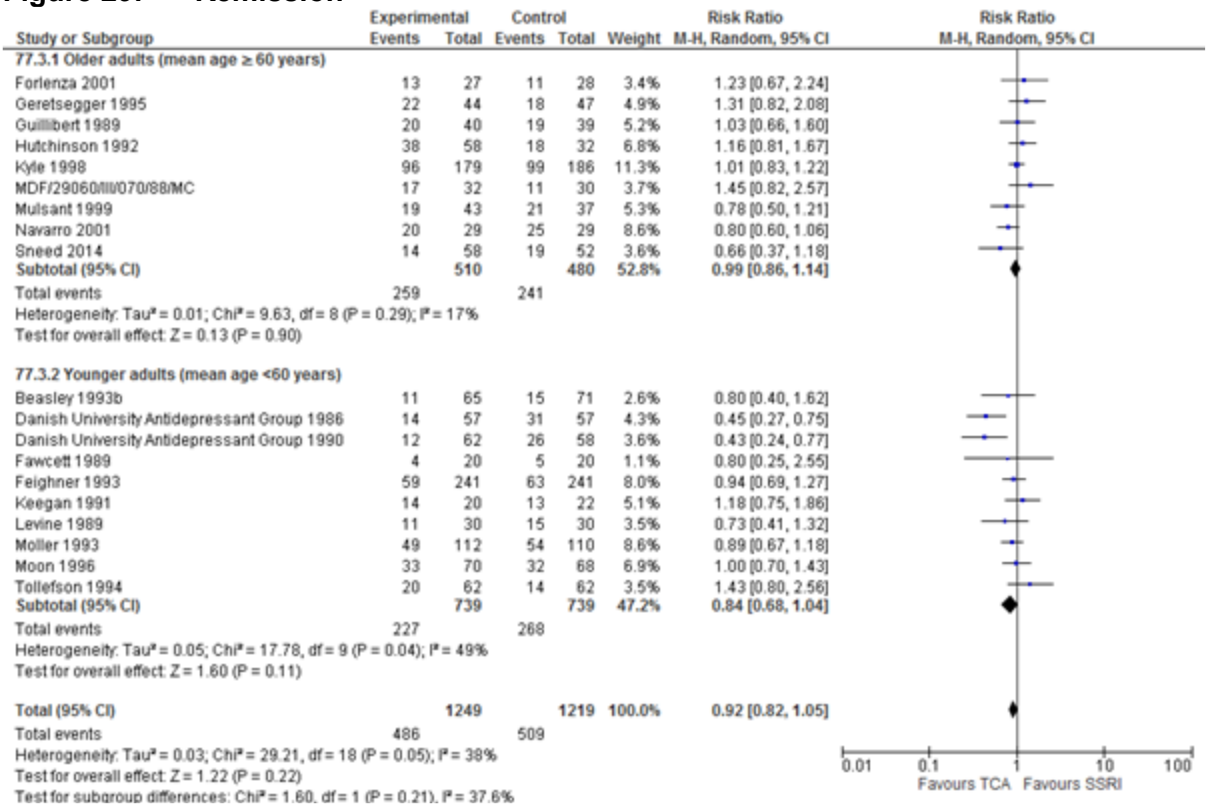


Figure 30: Response

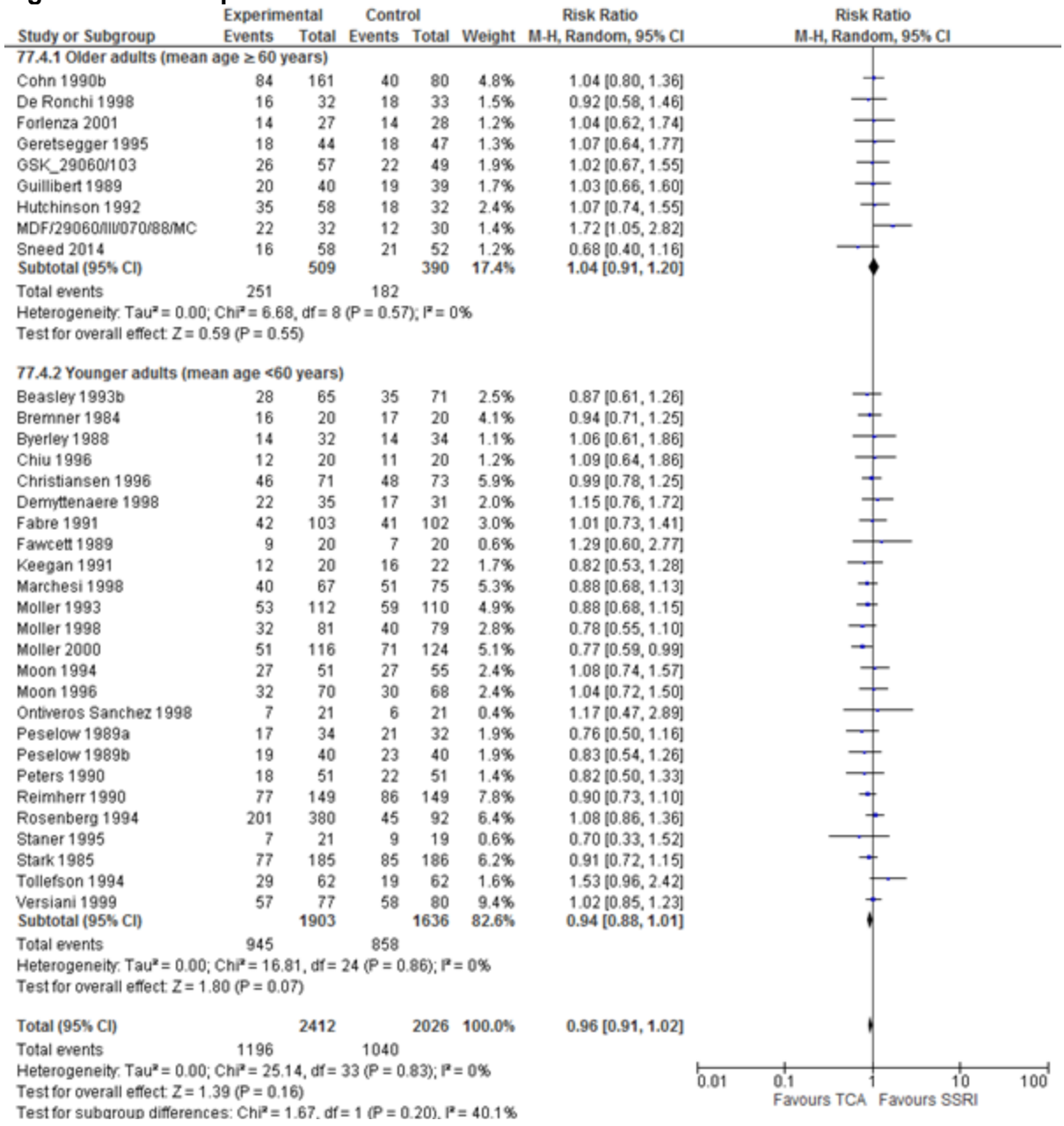


Figure 31: Discontinuation due to side effects

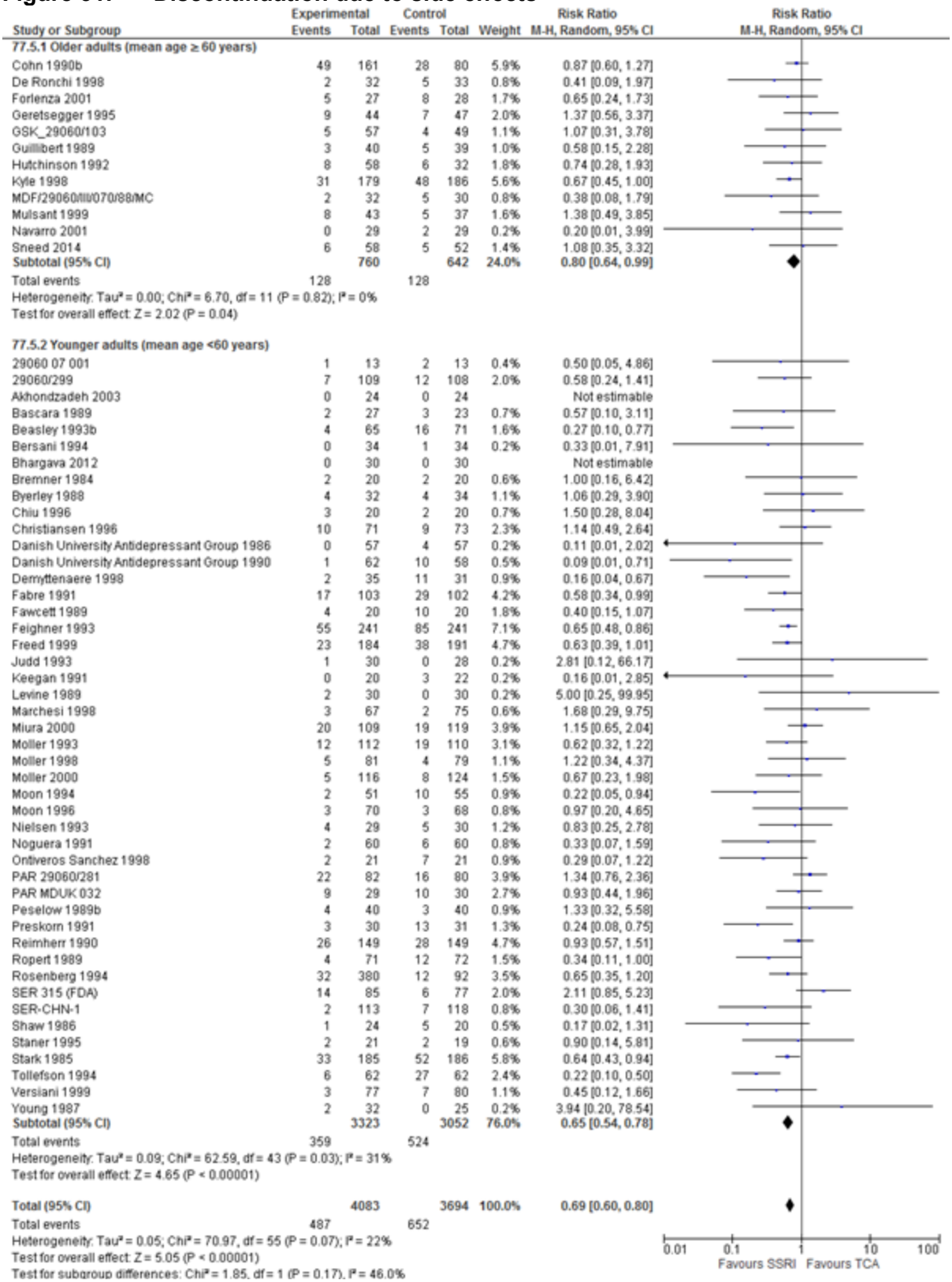
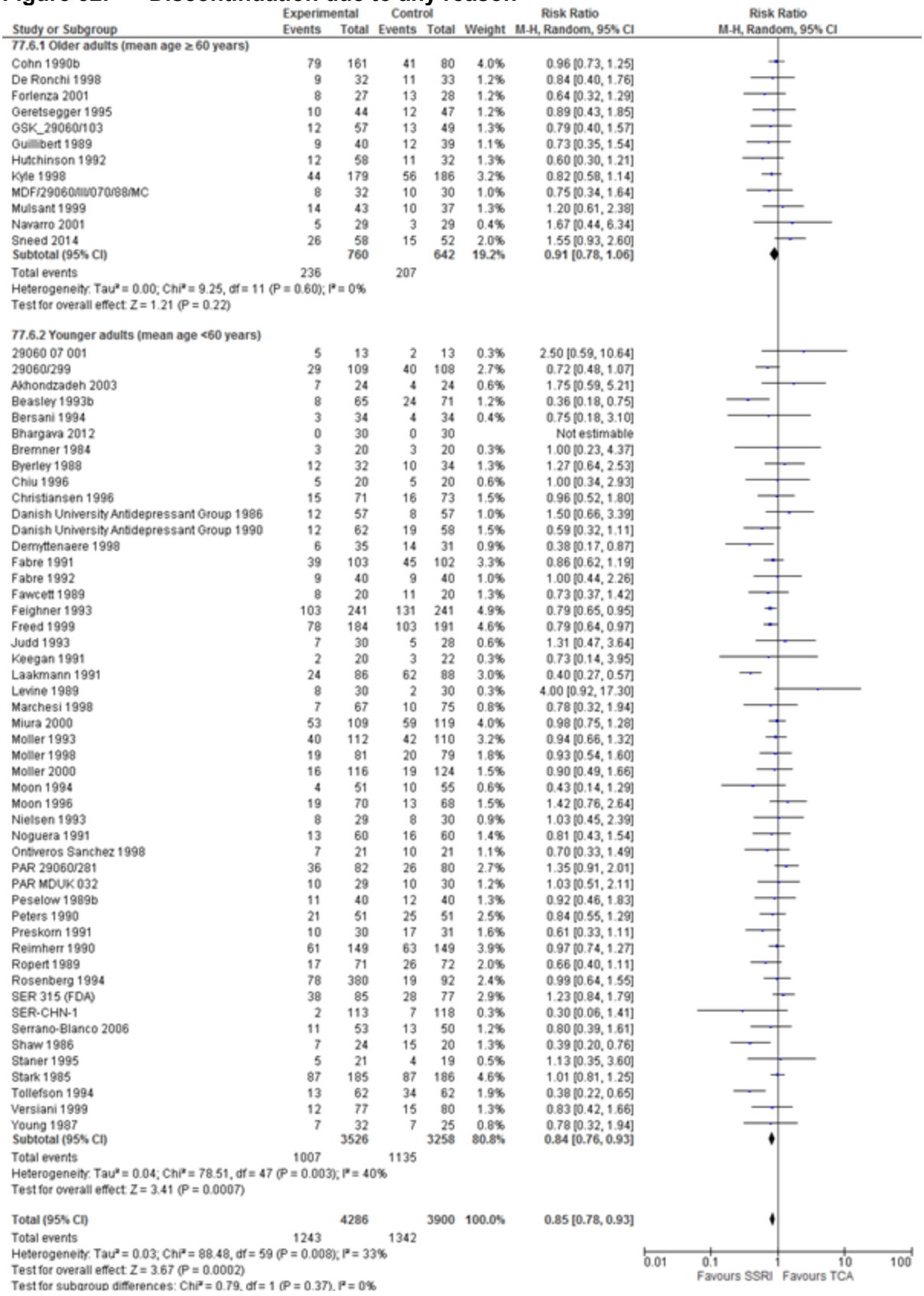


Figure 32: Discontinuation due to any reason



TCAs versus placebo

Figure 33: Remission

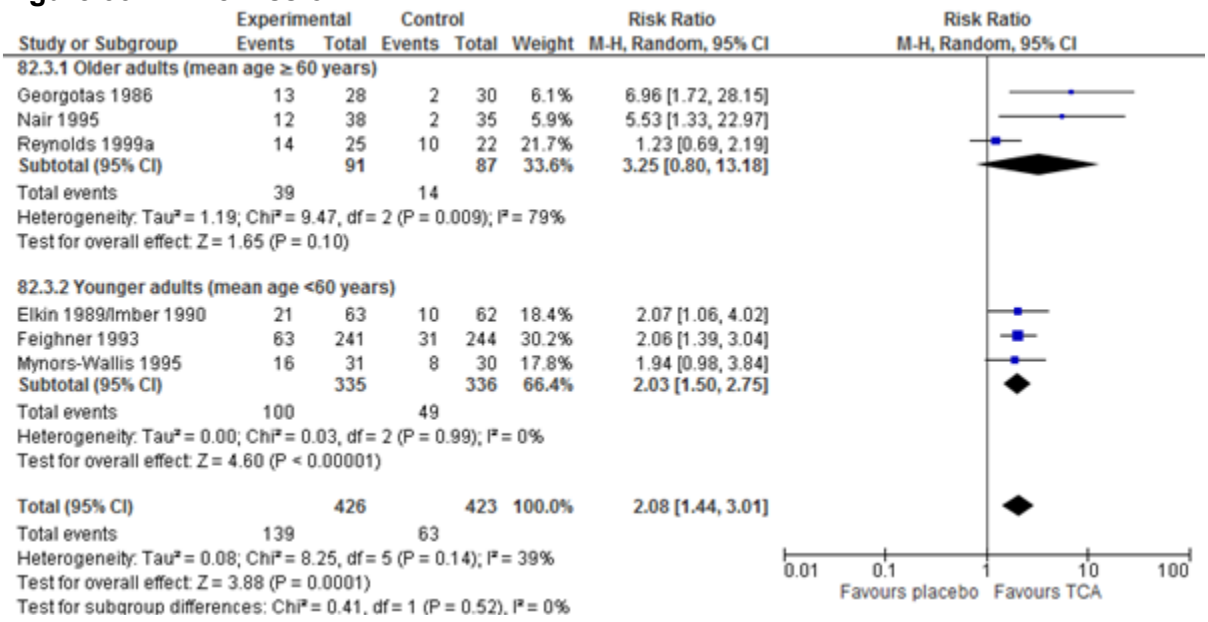


Figure 34: Response

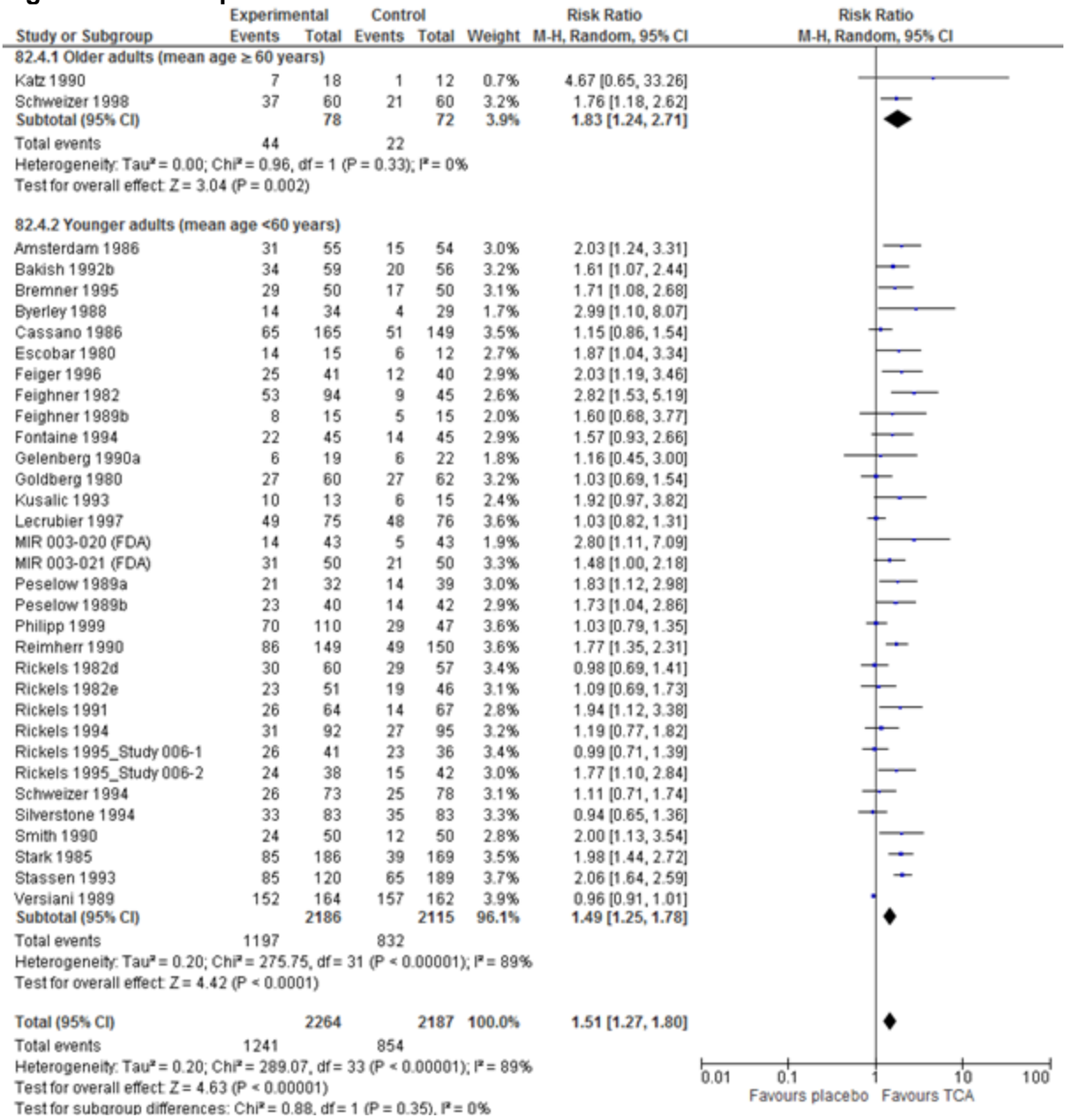


Figure 35: Discontinuation due to side effects

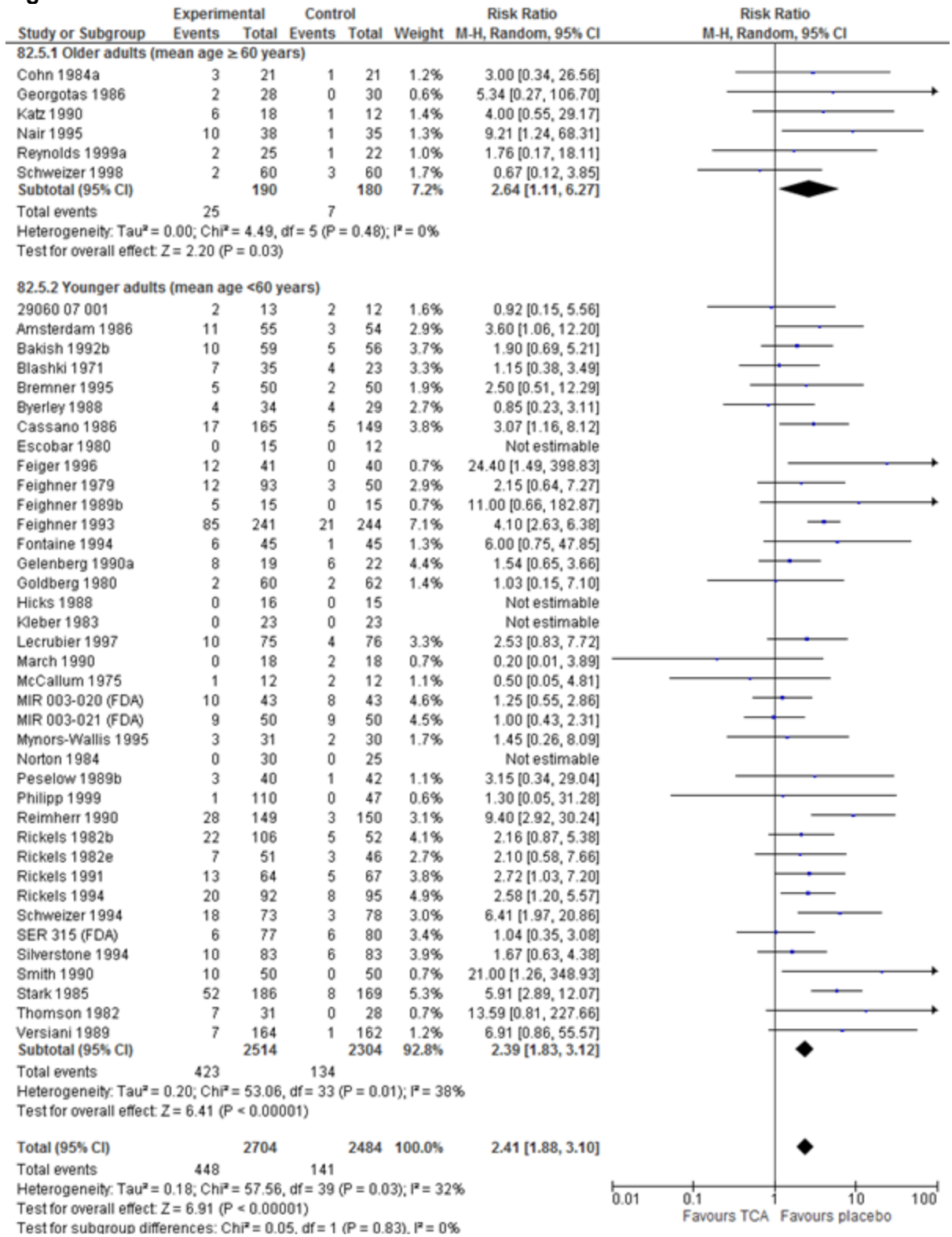
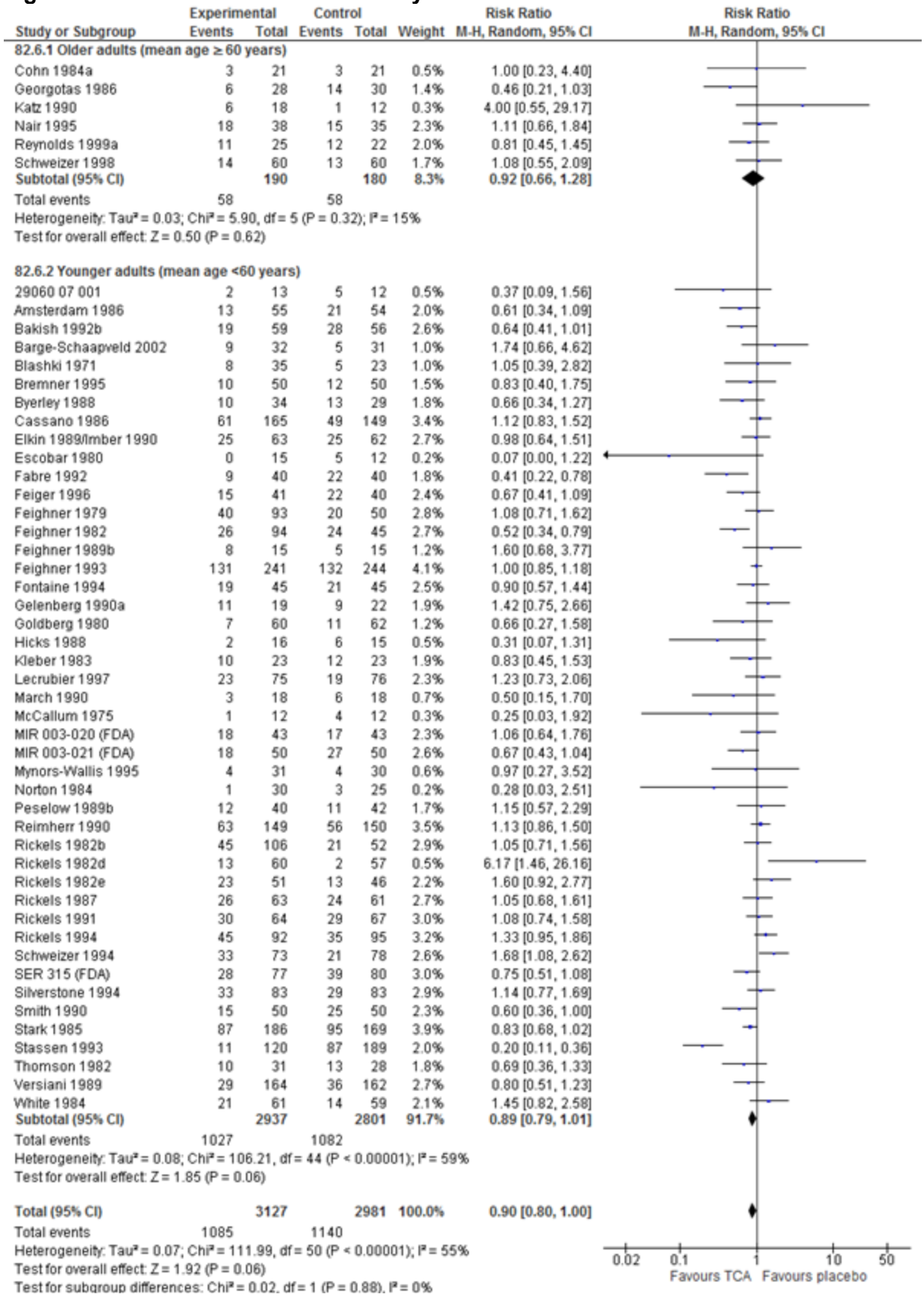


Figure 36: Discontination due to any reason



SNRIs versus placebo

Figure 37: Depression symptoms change score

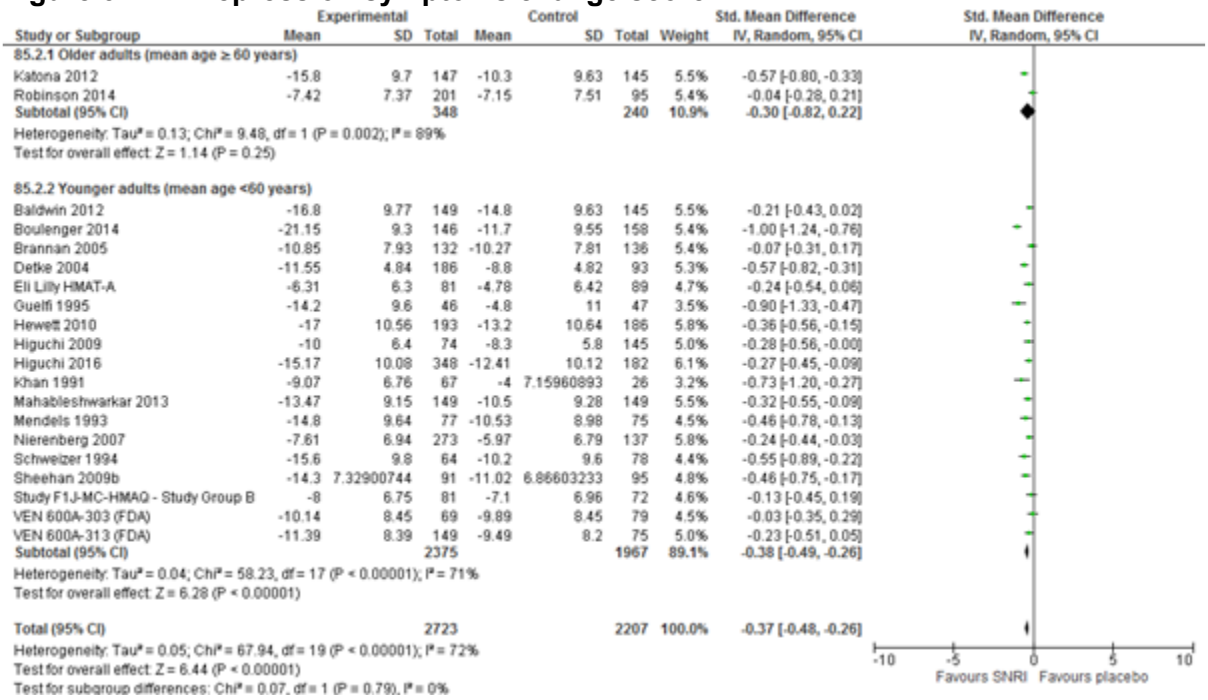


Figure 38: Remission

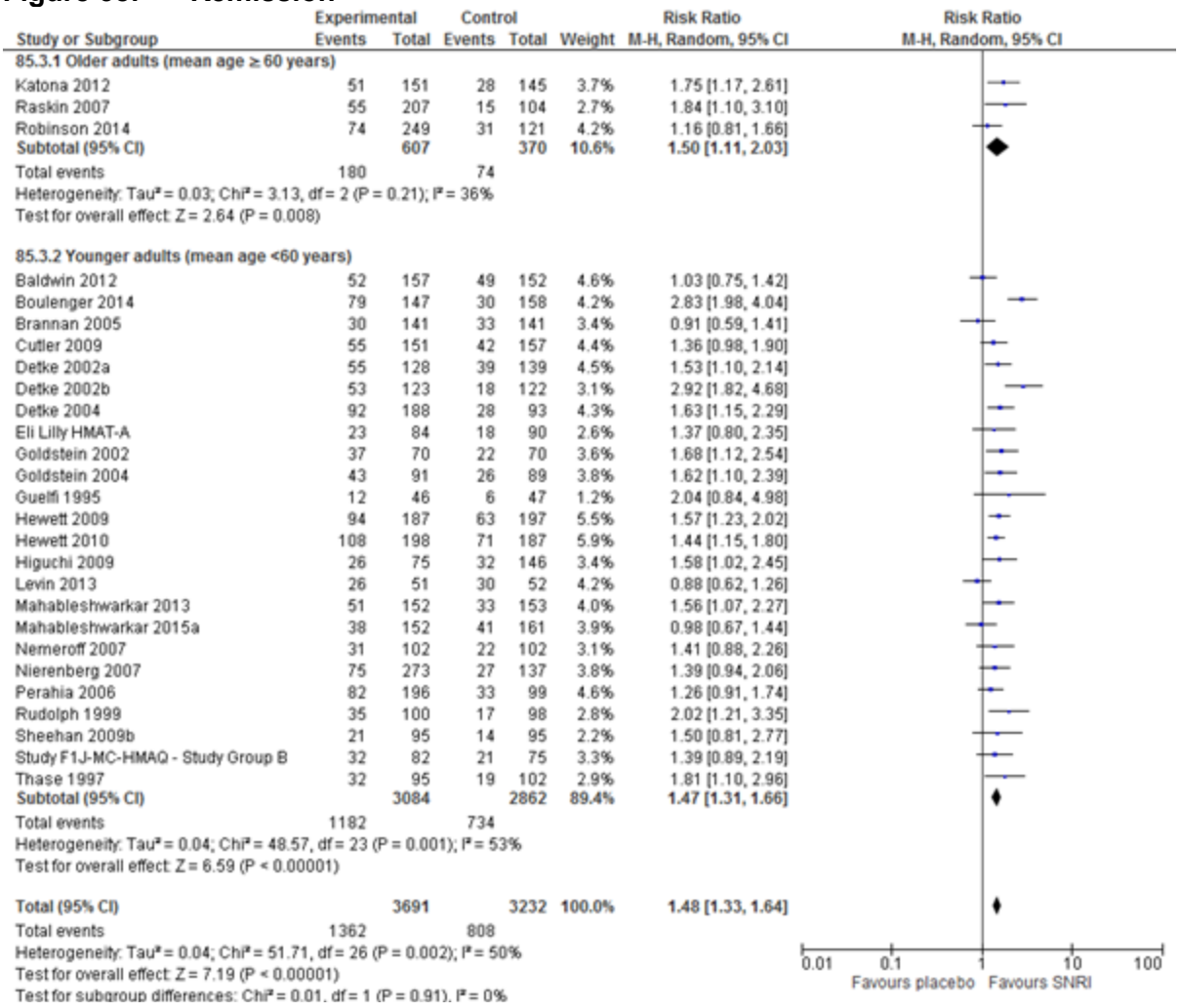


Figure 39: Response

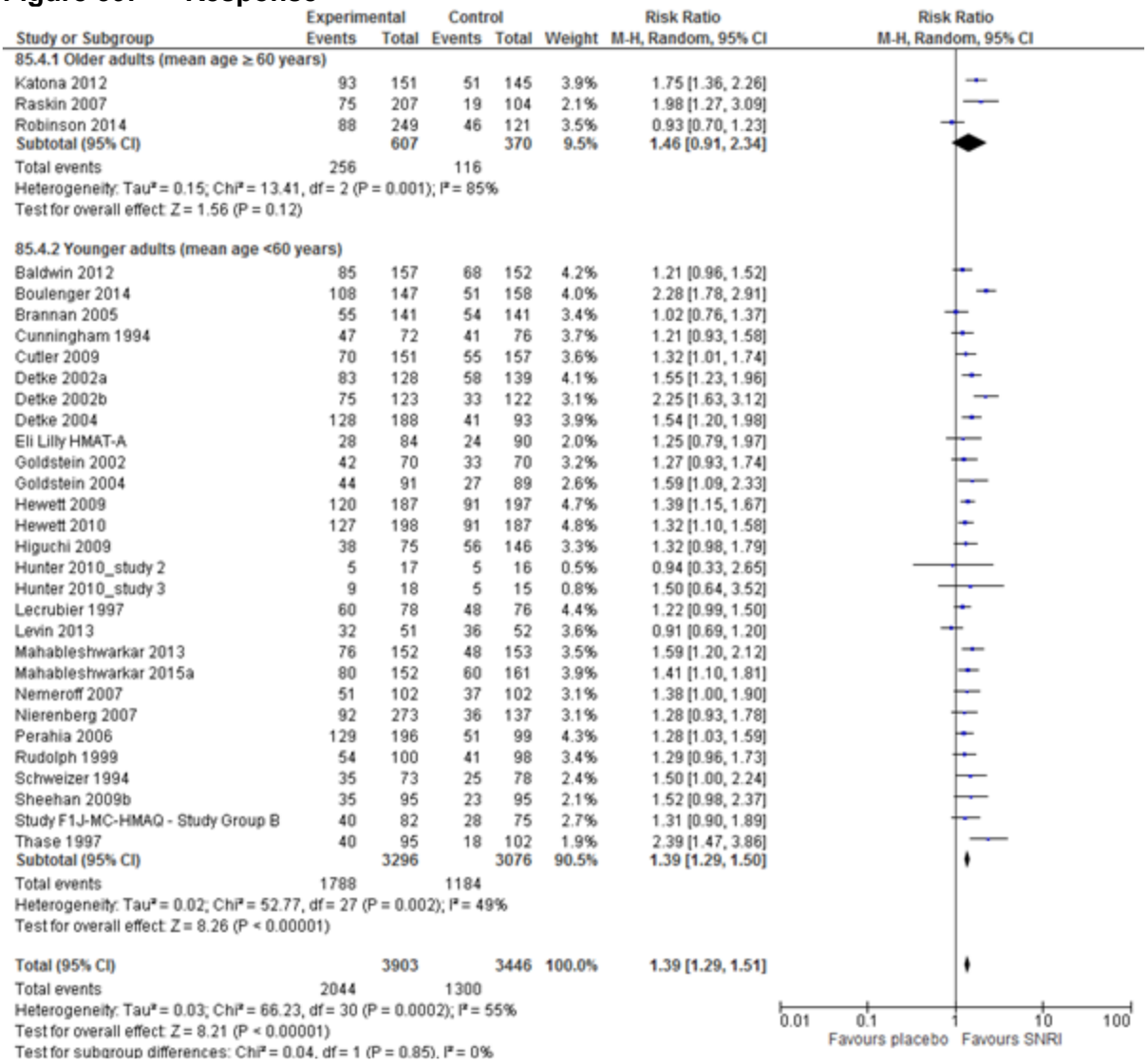


Figure 40: Dicontinuation due to side effects

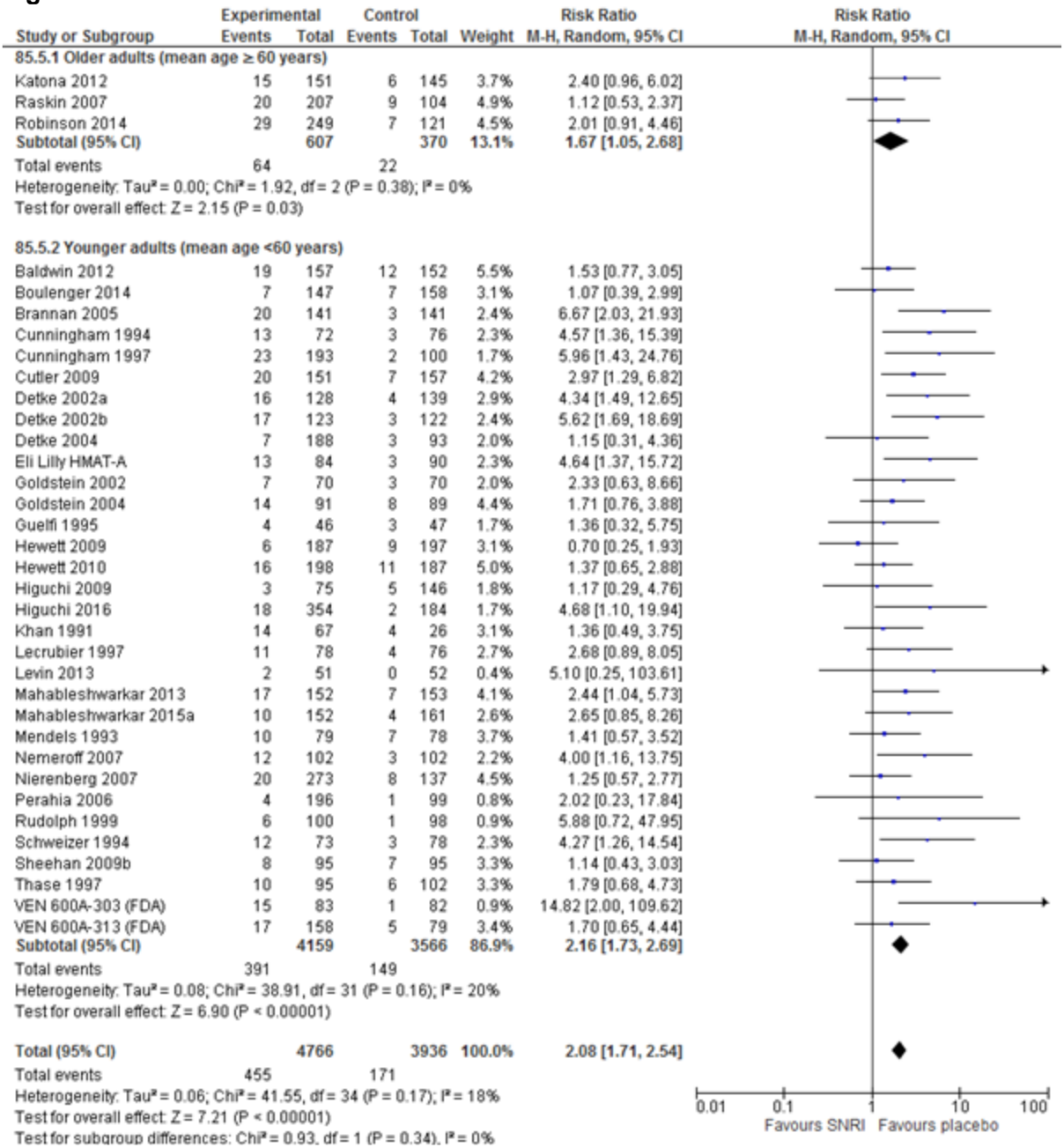
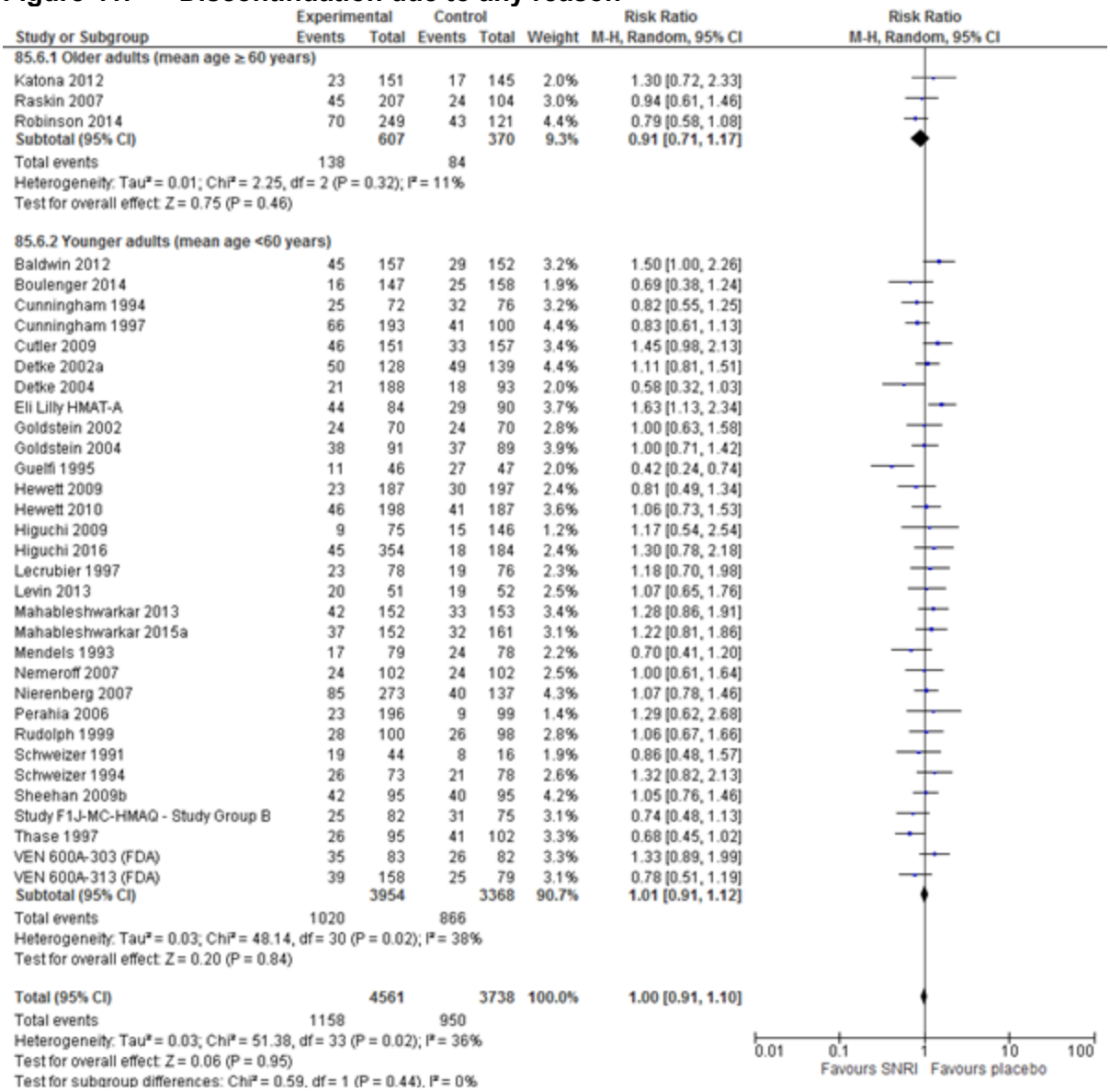


Figure 41: Discontinuation due to any reason



SNRIs versus TCAs

Figure 42: Discontinuation due to side effects

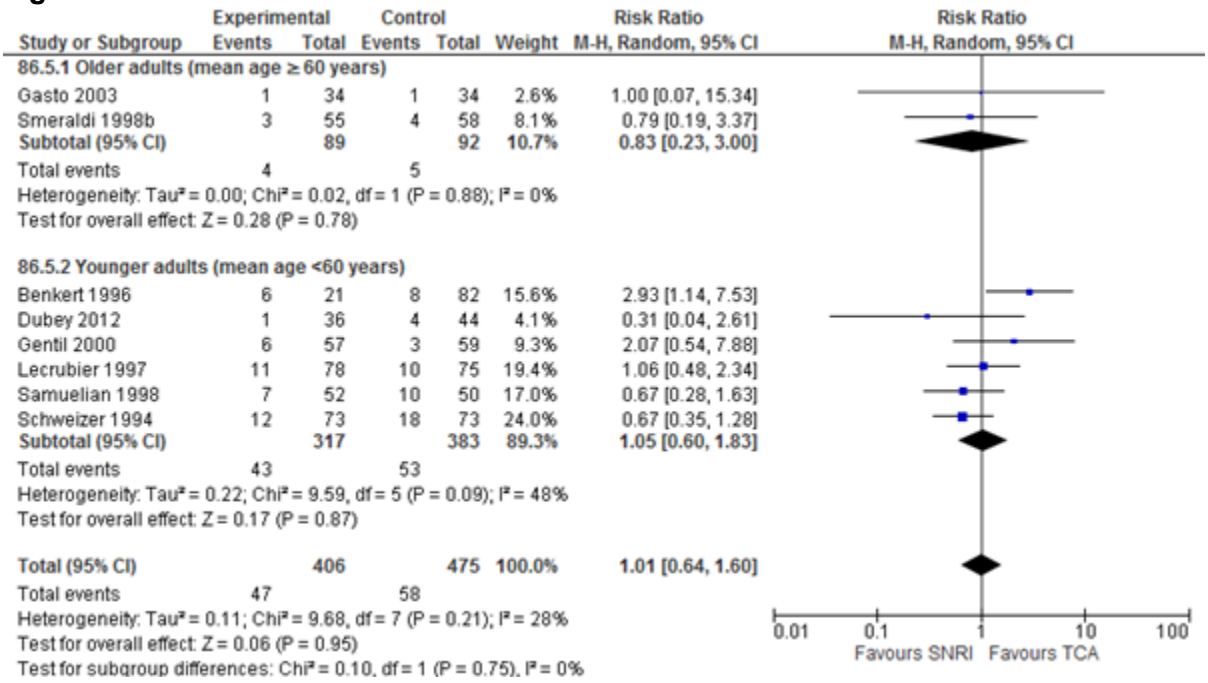
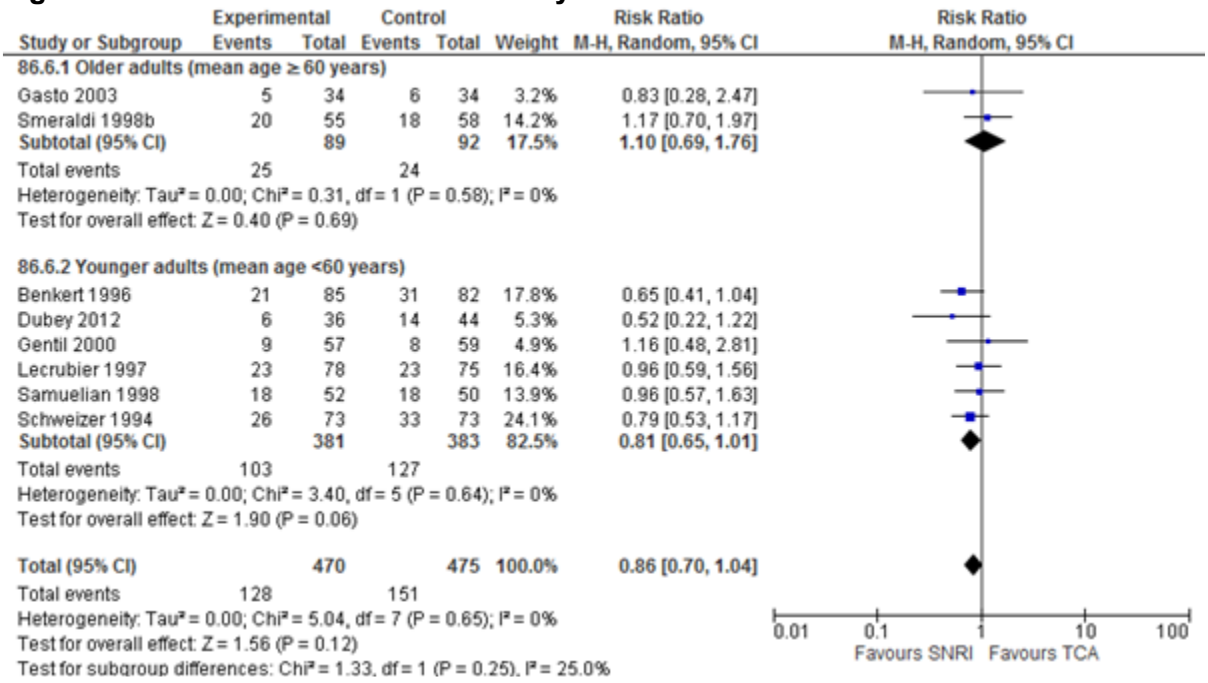


Figure 43: Discontinuation due to any reason



SNRIs versus SSRIs

Figure 44: Remission

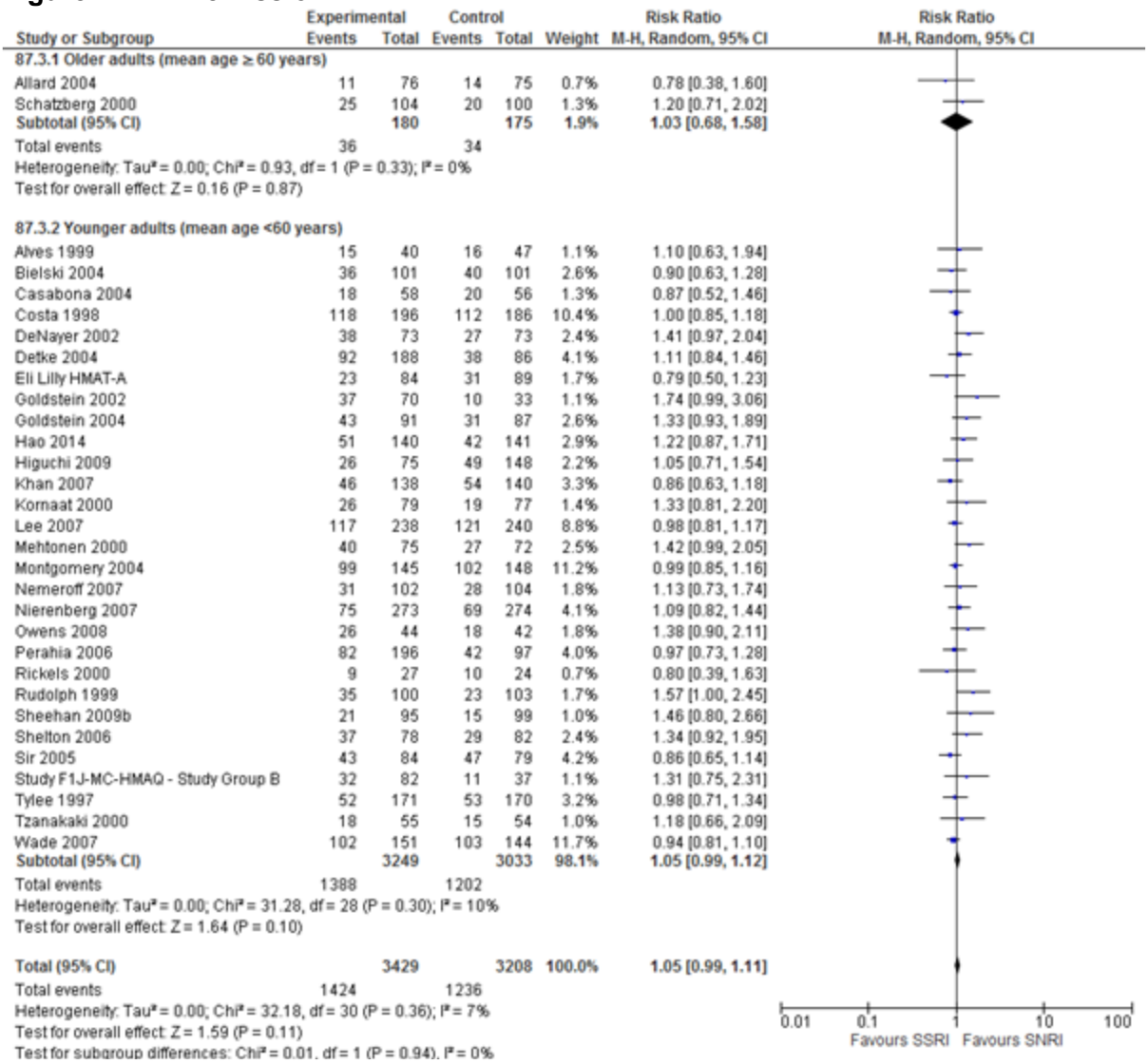


Figure 45: Response

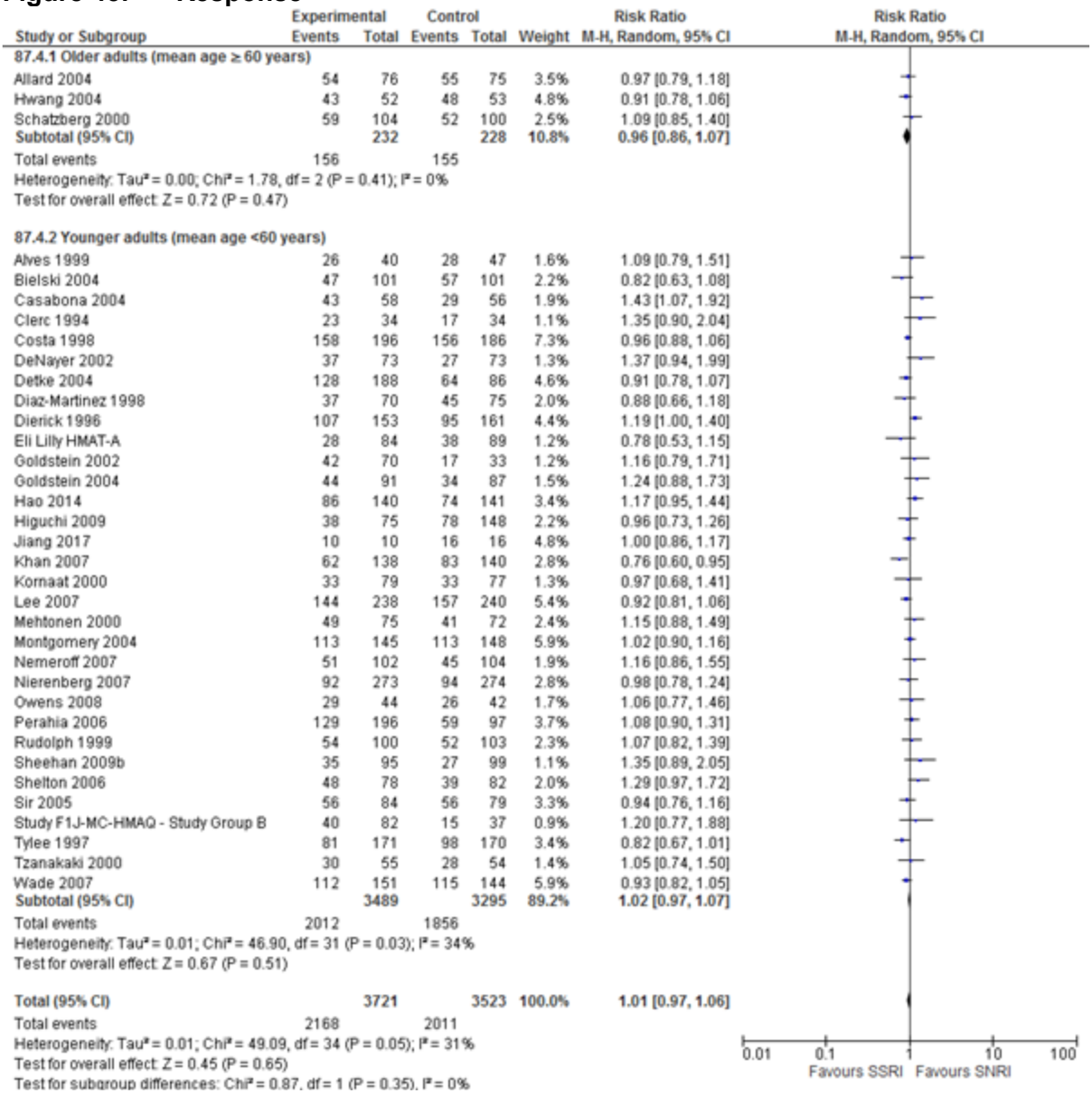


Figure 46: Discontinuation due to side effects

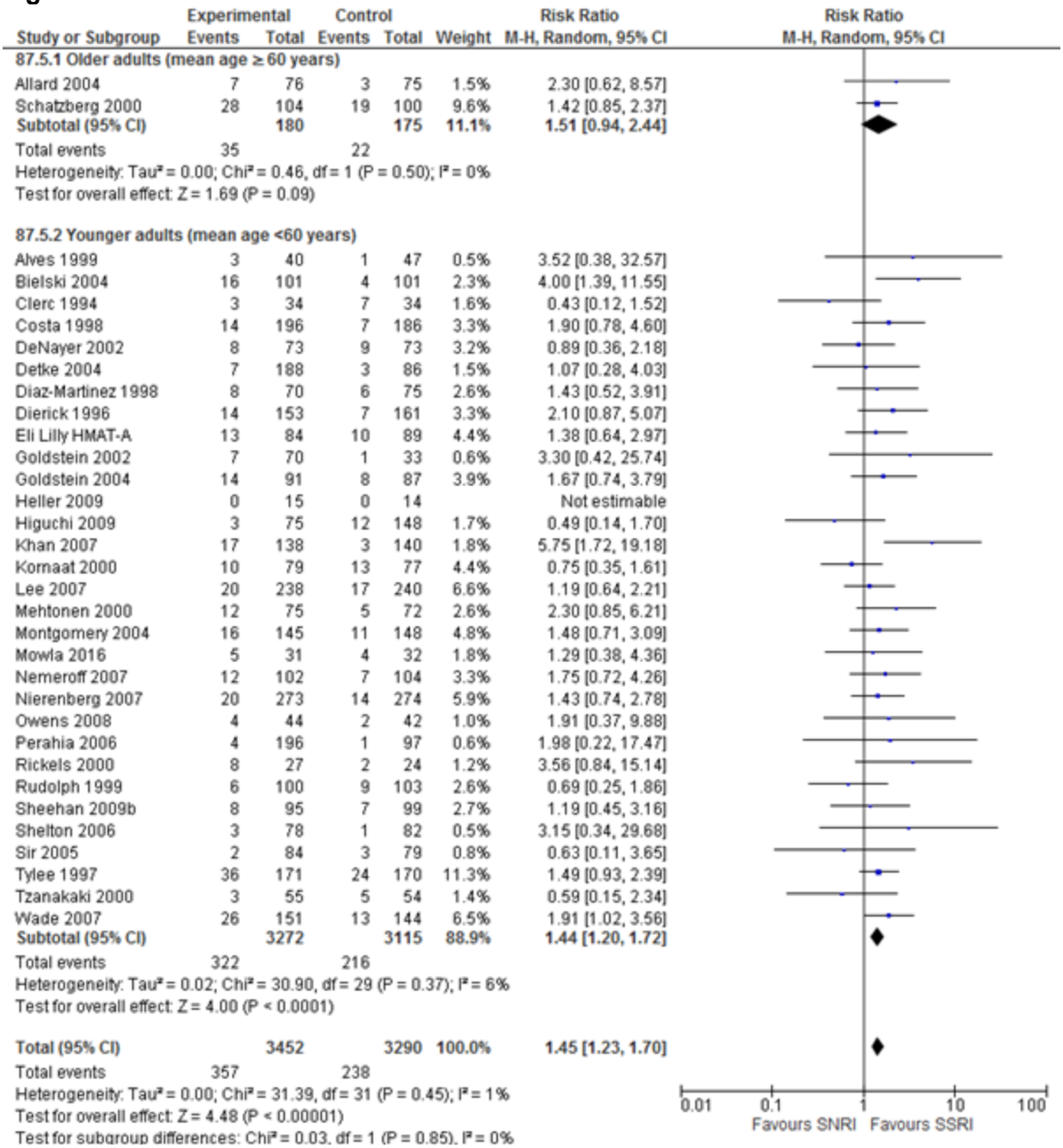
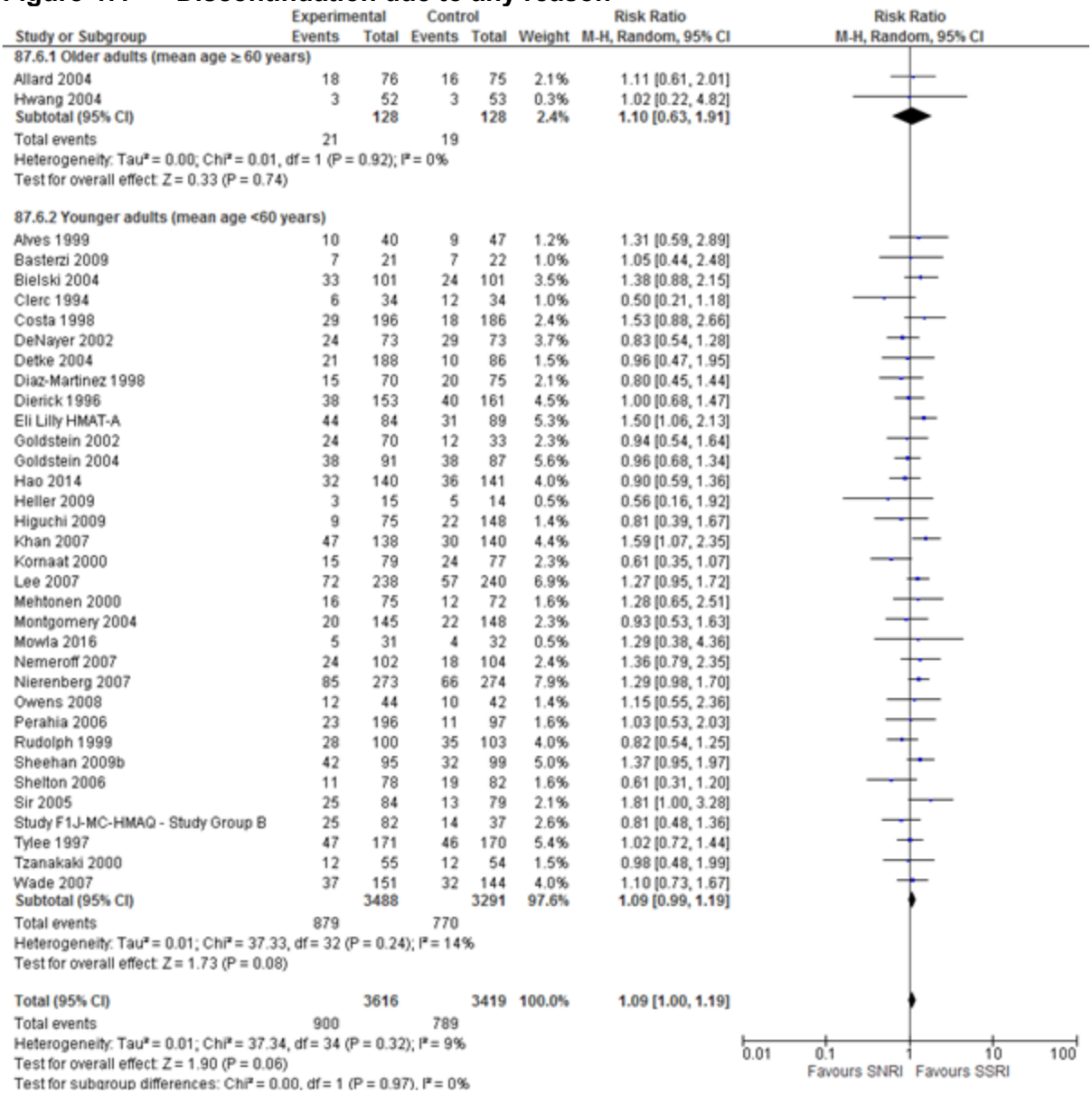


Figure 47: Discontinuation due to any reason



Trazodone versus TCAs

Figure 48: Discontinuation due to side effects

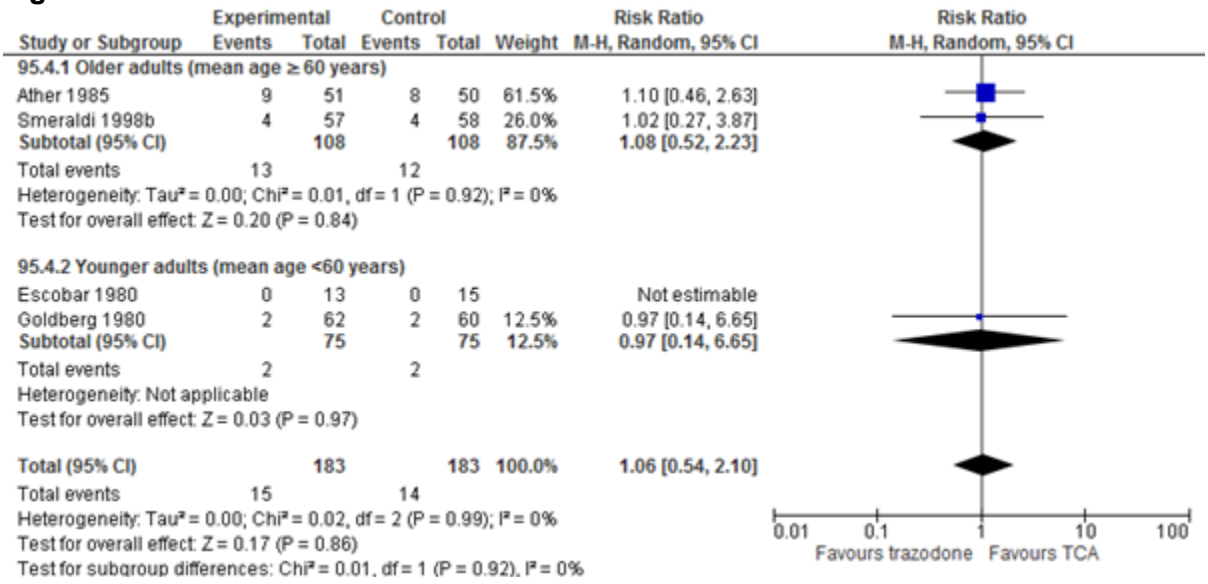
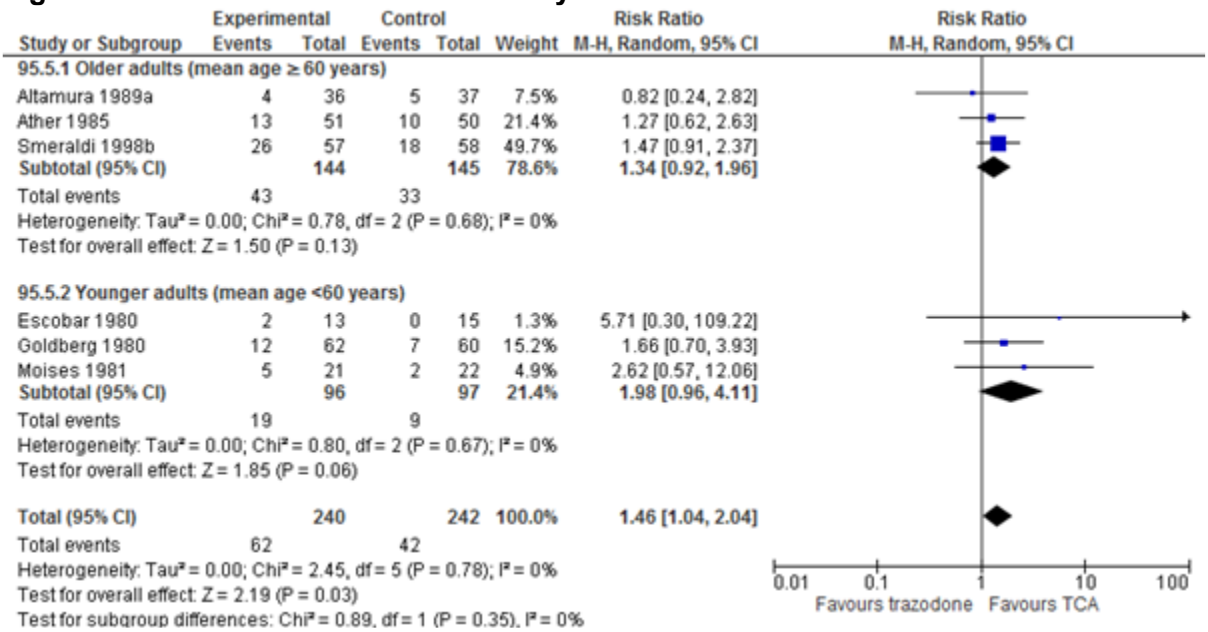


Figure 49: Discontinuation due to any reason



Pairwise meta-analysis of couple interventions (not included in the NMA)

Behavioural couples therapy versus waitlist

Figure 50: Depression symptoms endpoint

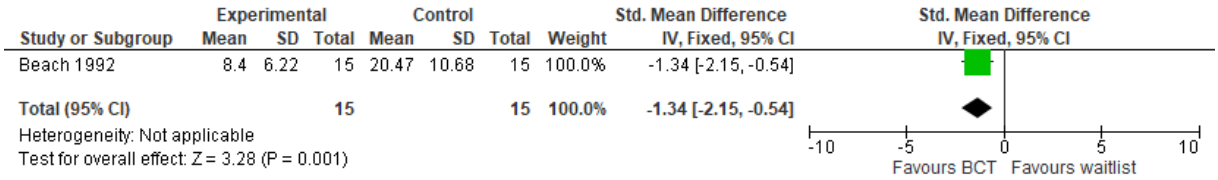


Figure 51: Depression symptoms change score

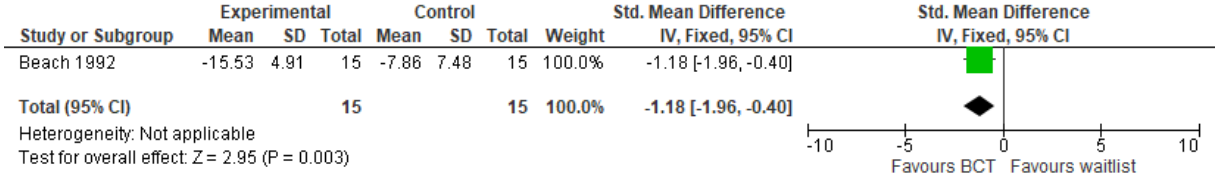


Figure 52: Marital adjustment endpoint

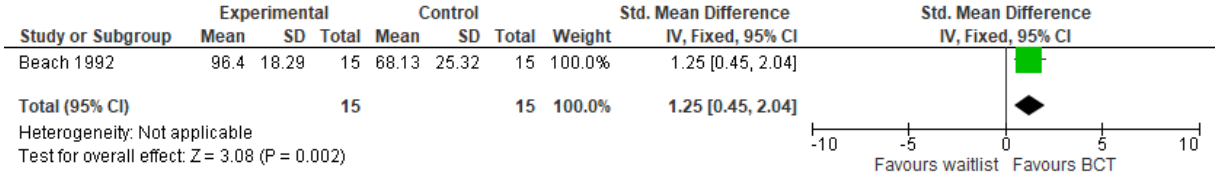
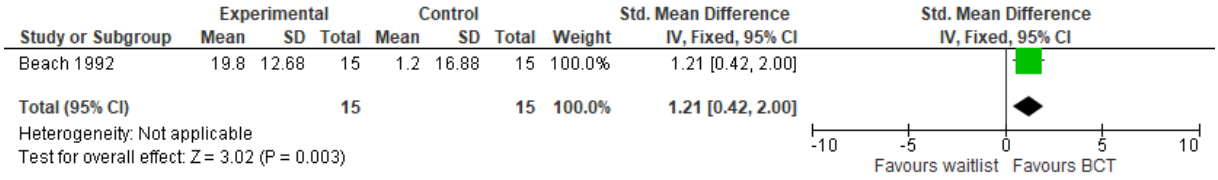


Figure 53: Marital adjustment change score



Behavioural couples therapy versus CBT individual

Figure 54: Depression symptoms endpoint

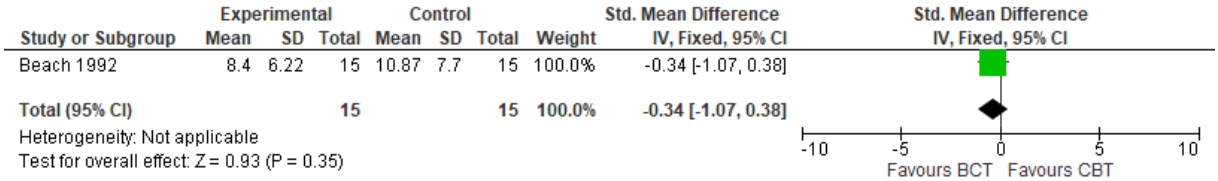


Figure 55: Depression symptoms change score

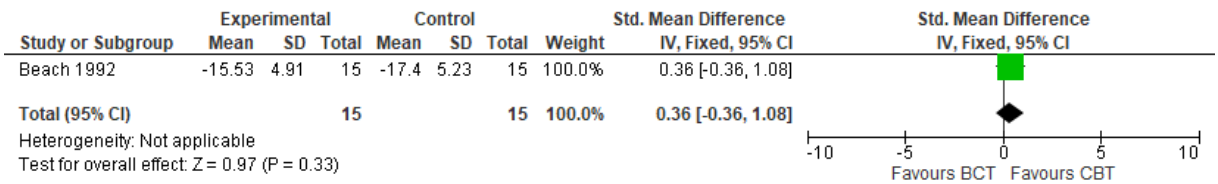


Figure 56: Marital adjustment endpoint

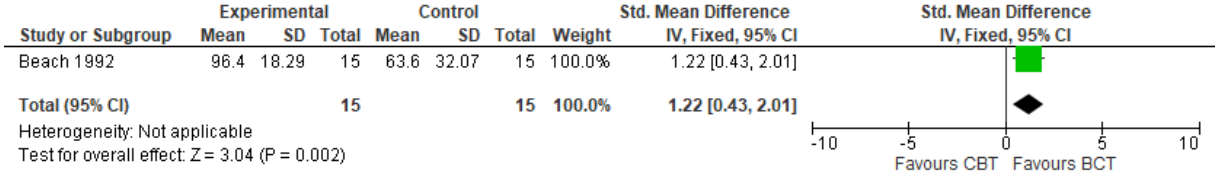
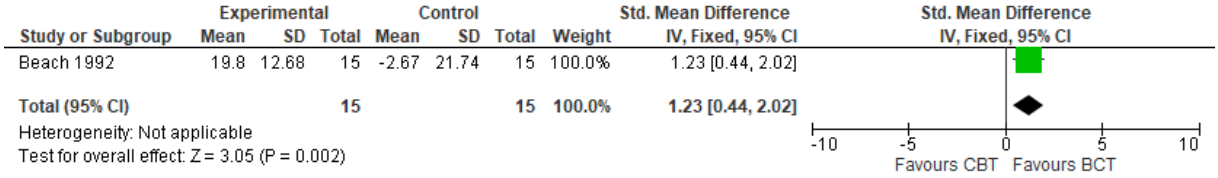


Figure 57: Marital adjustment change score



CBT individual versus waitlist

Figure 58: Depression symptoms endpoint

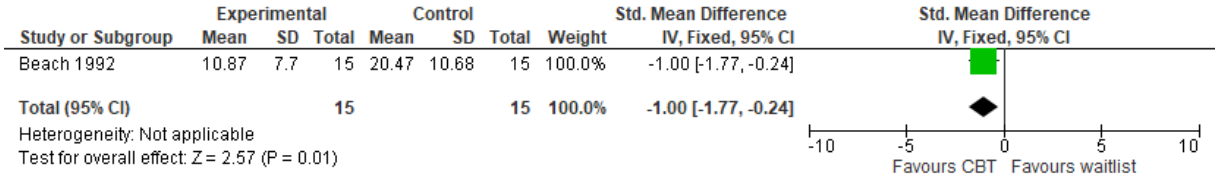


Figure 59: Depression symptoms change score

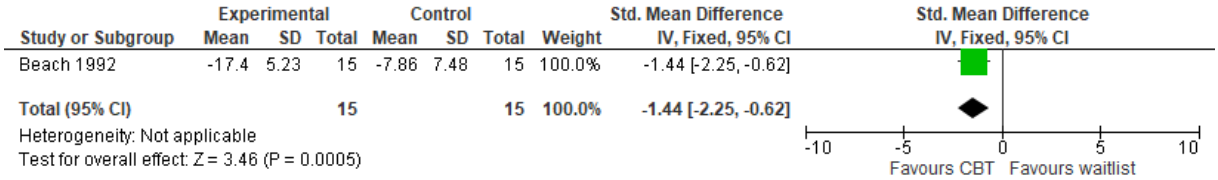


Figure 60: Marital adjustment endpoint

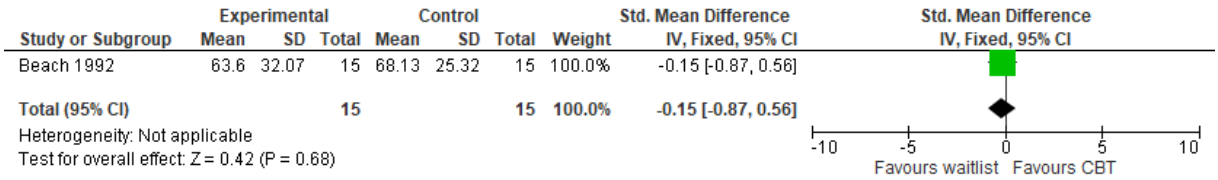
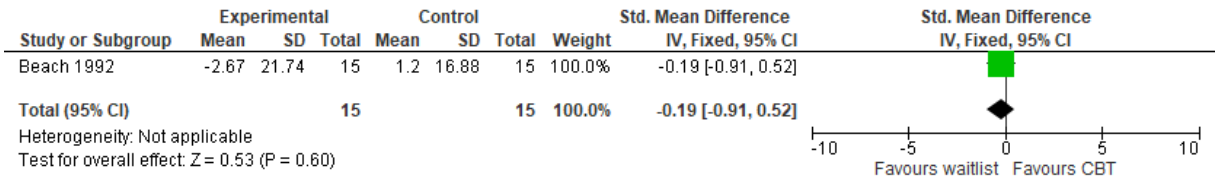


Figure 61: Marital adjustment change score



Appendix F – GRADE tables

To evaluate the quality of the evidence of the NMAs undertaken to inform this review question, we report information about the factors considered in a GRADE profile (risk of bias, publication bias, imprecision, inconsistency, and indirectness) – see under 'Quality assessment of studies included in the evidence review'.

GRADE table for pairwise meta-analysis of couple interventions (not included in NMA)

Table 34. Clinical evidence profile for comparison behavioural couples therapy versus waitlist

Quality assessment							Number of participants		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behavioural couples therapy	Waitlist	Relative (95% CI)	Absolute	Quality	Importance
Depression symptoms as measured by BDI change score (follow-up mean 15 weeks; better indicated by lower values)												
1 (Beach 1992)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	SMD 1.18 lower (1.96 to 0.4 lower)	-	VERY LOW	CRITICAL
Marital adjustment as measured by DAS change score (follow-up mean 15 weeks; better indicated by higher values)												
1 (Beach 1992)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	SMD 1.21 higher (0.42 to 2.00 higher)	-	VERY LOW	IMPORTANT

Abbreviations. BDI: Beck Depression Inventory; DAS: Dyadic Adjustment Scale
1 Very serious risk of bias due to unclear risk of selection bias (unclear randomisation method and unclear allocation concealment method), high risk of performance bias (non-blind), unclear risk of detection bias (blinding of outcome assessor unclear), unclear risk of attrition bias (drop-out not reported), and high risk of selective reporting bias (discontinuation not reported, and follow-up data cannot be extracted)
2 Imprecision downgraded by 1 level as the 95% confidence interval crosses thresholds for both clinically important benefit and no effect

Table 35. Clinical evidence profile for comparison behavioural couples therapy versus CBT individual

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Behavioural couples therapy**	**CBT individual**	**Relative (95% CI)**	**Absolute**		
Depression symptoms as measured by BDI change score (follow-up mean 15 weeks; better indicated by lower values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	SMD 0.36 higher (0.36 lower to 1.08 higher)	-	VERY LOW	CRITICAL
Marital adjustment as measured by DAS change score (follow-up mean 15 weeks; better indicated by higher values)												
1	randomised trials	very serious 1	no serious inconsistency	no serious indirectness	serious2	none	15	15	SMD 1.23 higher (0.44 to 2.02 higher)	-	VERY LOW	IMPORTANT

Abbreviations. BDI: Beck Depression Inventory; DAS: Dyadic Adjustment Scale
1 Very serious risk of bias due to unclear risk of selection bias (unclear randomisation method and unclear allocation concealment method), high risk of performance bias (non-blind), unclear risk of detection bias (blinding of outcome assessor unclear), unclear risk of attrition bias (drop-out not reported), and high risk of selective reporting bias (discontinuation not reported, and follow-up data cannot be extracted)
2 Imprecision downgraded by 1 level as the 95% confidence interval crosses thresholds for both clinically important benefit and no effect

Table 36. Clinical evidence profile for comparison CBT individual versus waitlist

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBT individual**	**Waitlist**	**Relative (95% CI)**	**Absolute**		
Depression symptoms as measured by BDI change score (follow-up mean 15 weeks; better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	15	SMD 1.44 lower (2.25 to 0.62 lower)	-	LOW	CRITICAL
Marital adjustment as measured by DAS change score (follow-up mean 15 weeks; better indicated by higher values)												

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT individual	Waitl ist	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	15	SMD 0.19 lower (0.91 lower to 0.52 higher)	-	VERY LOW	IMPORTANT

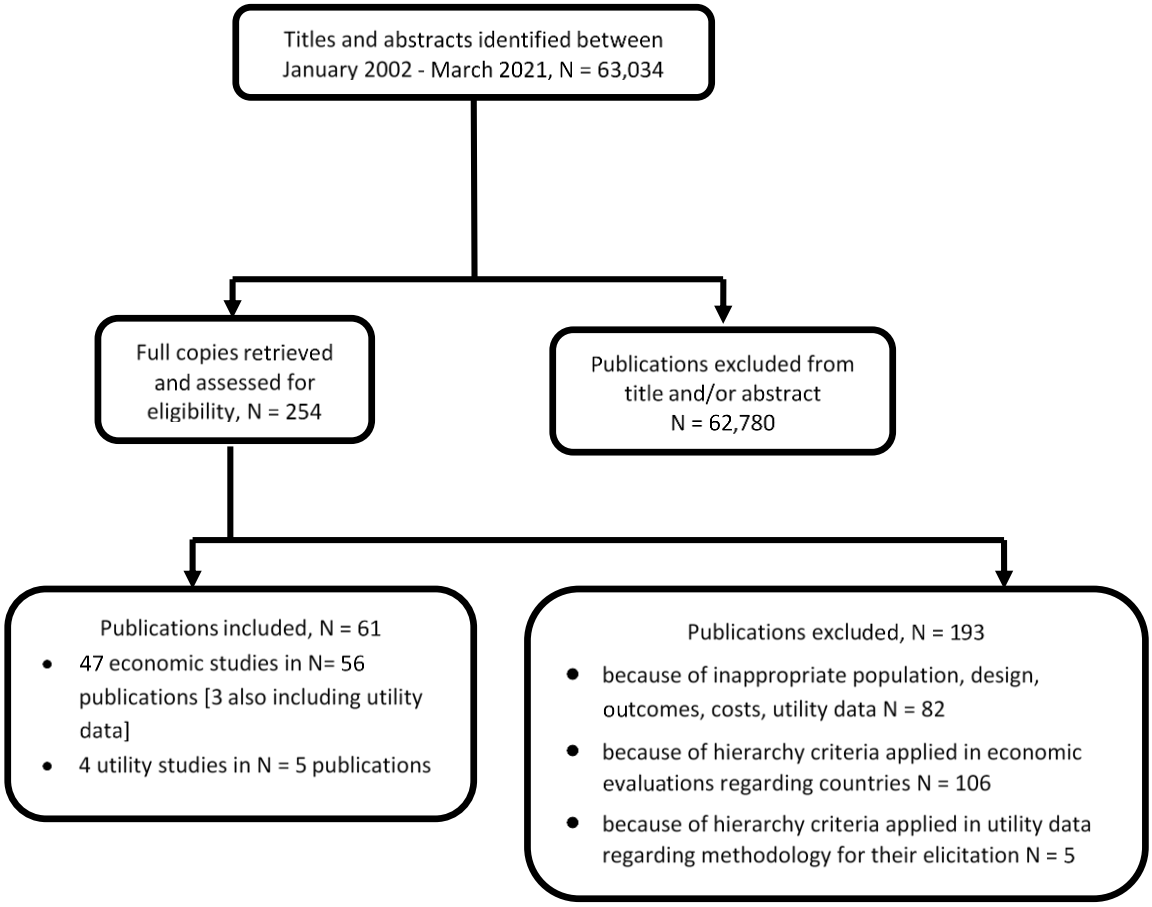
Abbreviations. BDI: Beck Depression Inventory; DAS: Dyadic Adjustment Scale
1 Very serious risk of bias due to unclear risk of selection bias (unclear randomisation method and unclear allocation concealment method), high risk of performance bias (non-blind), unclear risk of detection bias (blinding of outcome assessor unclear), unclear risk of attrition bias (drop-out not reported), and high risk of selective reporting bias (discontinuation not reported, and follow-up data cannot be extracted)
2 Imprecision downgraded by 2 levels as 95% confidence interval crosses thresholds for both clinically important benefit and harm, and threshold for no effect

Appendix G – Economic evidence study selection

Economic evidence study selection for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

A global health economics search was undertaken for all areas covered in the guideline. Figure 62 shows the flow diagram of the selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data.

Figure 62. Flow diagram of selection process for economic evaluations of interventions and strategies for adults with depression and studies reporting depression-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 37. Economic evidence table for individual problem solving versus treatment as usual

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kendrick 2005/2006a UK Cost-utility analysis	Interventions: Problem-solving treatment provided by nurses Generic community mental health (MH) nurse care Usual GP care	Adults with a new episode of anxiety, depression or reaction to life difficulties with duration of symptoms 4 weeks to 6 months; and a General Health Questionnaire 12-item version (GHQ–12) ≥3. Exclusion criteria: current psychological treatment or contact with psychiatric services; severe mental disorder or substance misuse; dementia; active suicidal ideas Pragmatic RCT (N=247) (Kendrick 2005/2006a) Source of efficacy & resource use data: RCT, analysis based on n=184 with clinical data available; cost data available for n=159 Source of unit costs: national sources	Costs: intervention, training & supervision, medication, staff time (GP, practice nurse, counsellor, social worker, psychiatrist, psychologist), outpatient visit, A&E, inpatient care, other hospital contacts For societal perspective: out of pocket expenses and productivity losses Mean total NHS cost per person (SD): Problem solving: £608 (£501) MH nurse care: £569 (£350) GP care: £283 (£300) Adjusted differences vs GP care (95% CI): Problem solving: £325 (£204 to £484) MH nurse care: £286 (£174 to £411) Outcome measure: QALY based on EQ-5D ratings (UK tariff) Mean QALYs gained per person (SD): Problem solving: 0.39 (0.09) MH nurse care: 0.40 (0.07) GP care: 0.40 (0.07) Adjusted differences in QALY vs GP care (95% CI): Problem solving: -0.02 (-0.05 to 0.012) MH nurse care: 0 (-0.03 to 0.03)	NHS perspective: usual GP care dominant	Perspective: NHS (and societal) Currency: GBP£ Cost year: 2003 Time horizon: 26 weeks Discounting: NA Applicability: directly applicable Quality: minor limitations

Table 38. Economic evidence table for self-help: computerised cognitive behavioural therapy (CBT) versus treatment as usual

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kaltenthaler 2006 UK Cost-utility analysis	Interventions: Computerised CBT – 3 packages examined: Beating the Blues (cCBT1) Cope (cCBT2) Overcoming Depression (cCBT3) Treatment as usual, defined as GP visits, medication and possible referral to a specialist (TAU)	Adults with depression treated in a primary care setting Decision-analytic modelling Source of efficacy data: analysis of RCT individual-level data for cCBT1 and cCBT2; published RCT data for cCBT3; and further assumptions Source of resource use data: manufacturer submissions, published data and other assumptions Source of unit costs: national sources	Costs: intervention (licence fees, computer hardware, screening of patients for suitability, clinical support, capital overheads, training), healthcare costs according to severity of depression (including medication, primary, inpatient and outpatient care) Mean total cost per person: cCBT1: £584 cCBT2: £630 cCBT3: £501 TAU: £437 Outcome measure: QALY estimated based on EQ-5D (UK tariff) Mean QALYs per person cCBT1: 1.10 cCBT2: 1.05 cCBT3: 1.03 TAU: 1.02	ICER vs TAU: cCBT1: £1,801/QALY cCBT2: £7,139/QALY cCBT3: £5,391/QALY Probability of each intervention being cost-effective vs TAU at WTP £30,000/QALY: cCBT1: 0.87 cCBT2: 0.63 cCBT3: 0.54	Perspective: NHS Currency: GBP£ Cost year: likely 2003 Time horizon: 18 months Discounting: 3.5% annually Applicability: directly applicable Quality: potentially serious limitations

Table 39. Economic evidence tables for SSRIs (sertraline) versus placebo

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Hollingworth 2020 UK	Interventions: Sertraline Placebo	Adults aged 18-74 years presenting to primary care with depression or low mood during the past 2 years who had	Costs: sertraline, primary care consultations and phone calls (GP, nurse), medication, inpatient and outpatient care, accident and emergency, community care, home visits, other community care	Imputed incremental net monetary benefit (95% CI) at WTP £20,000 /QALY: whole sample: £122 (£18 to £226)	Perspective: NHS & personal social services Currency: GBP£

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Cost-utility analysis		not received antidepressant or anti-anxiety medication in the previous 8 weeks. Pragmatic RCT (N=655) (Lewis 2019) Source of efficacy & resource use data: RCT, analysis based on data imputation. n=505 with utility (EQ-5D) data available; cost data available for n=381 Source of unit costs: national sources	Mean imputed total cost /person (SD): Sertraline: £154 (£19) Placebo: £177 (£26) Difference: −£22 (−£87 to £42) Sub-group with mild depression: Difference: −£19 (−£154 to £116) Sub-group with moderate depression: Difference: £4 (−£145 to £152) Sub-group with severe depression: Difference: −£41 (−£109 to £27) Outcome measure: QALY estimated based on EQ-5D (UK tariff) Mean imputed QALYs / person (SD): Sertraline: 0.182 (0.002) Placebo: 0.177 (0.002) Difference: 0.005 (−0.003 to 0.012) Sub-group with mild depression: Difference: 0.004 (−0.004 to 0.012) Sub-group with moderate depression: Difference: 0.007 (0 to 0.014) Sub-group with severe depression: Difference: 0.005 (−0.002 to 0.011)	Sub-group with mild depression: £102 (−£114 to £317) Sub-group with moderate depression: £135 (−£69 to £339) Sub-group with severe depression: £131 (−£18 to £281) Probability of sertraline being cost-effective at WTP £20,000 /QALY: >95% in whole sample; >70% in each sub-group	Cost year: 2018 Time horizon: 12 weeks Discounting: NA Applicability: directly applicable Quality: minor limitations

Table 40. Economic evidence tables for SSRIs added to treatment as usual versus treatment as usual alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Kendrick 2009 UK	Interventions: SSRIs (fluoxetine,	Adults with depressive symptoms for ≥ 8 weeks, who had received no	Costs: medication, primary care (face-to-face GP consultations, GP telephone contacts, practice nurse contacts), secondary care (inpatient,	At 12 weeks SSRI & GP dominates GP alone	Perspective: health and social care

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Cost effectiveness and cost-utility analysis	fluvoxamine, sertraline, paroxetine, citalopram or escitalopram) plus GP supportive care GP supportive care alone, comprising consultations at 2, 4, 8 and 12 weeks after the baseline assessment	antidepressant treatment within the previous 12 months, were not in receipt of counselling or psychological therapies at baseline, had a baseline HAMD17 score 12-19 and at least one symptom on the Bradford Somatic Inventory (BSI). Exclusion criteria: significant substance misuse and an Alcohol Use Disorders Identification Test (AUDIT) score ≥ 12 RCT (Kendrick2009, N=220) Source of efficacy & resource use data: RCT (N=220; 12-week completers n=196; 6-month followed-up n=160) Source of unit costs: national sources	outpatient, day patient, accident and emergency), community health services (health visitors, district nurses, counselling or psychological therapists), social care services (social workers, housing workers) Mean (SD) total cost per person: At 12 weeks: SSRI & GP: £341 (£454); GP alone: £388 (£932) Difference adjusted for baseline: -£28 (95%CI -£656 to £117) At 26 weeks: SSRI & GP: £759 (£1730); GP alone: £629 (£1092) Difference adjusted for baseline: £153 (95%CI -£500 to £304) Outcome measures: HAMD17 score; QALY based on SF-36 ratings (UK tariff) Mean (SD) HAMD17 score per person: At 12 weeks SSRI & GP: 8.73 (5.20); GP alone: 11.22 (5.78) At 26 weeks SSRI & GP: 7.92 (5.67); GP alone: 9.73 (5.57) Mean QALYs gained per person: From baseline to 12 weeks SSRI & GP 0.159; GP alone 0.152 Difference adjusting for baseline 0.005 From baseline to 26 weeks	At zero WTP per unit of reduction on HAMD17, probability of SSRI & GP being cost-effective was 54.9% At a WTP of £20,000–£30,000/QALY, probability of SSRI & GP being cost-effective was 80-85%. At 26 weeks ICER of SSRI & GP vs. GP alone £90/unit of improvement on HAMD17 or £14,854/QALY SSRI & GP has a greater than 0.50 probability of being cost-effective when the WTP exceeds £80 per unit reduction on HAMD17 At a WTP at £20,000–£30,000/QALY, probability of SSRI & GP being cost-effective was 0.65-0.75	Currency: UK£ Cost year: 2007 Time horizon: 12 and 26 weeks Discounting: NA Applicability: directly applicable Quality: minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			SSRI & GP 0.331; GP alone 0.318 Difference adjusted for baseline 0.010		

Table 41. Economic evidence table for SSRIs versus TCAs: SSRIs versus TCAs versus lofepramine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Peveler 2005 / Kendrick 2006b UK Cost effectiveness and cost-utility analysis	Interventions: TCAs (amitriptyline, dothiepin or imipramine) SSRIs (fluoxetine, sertraline or paroxetine) Lofepramine (LOF) Treatment lasted 6 months after remission or for at least 12 months if participant had experienced ≥ 2 depressive episodes within the past 5 years.	Adults with a new episode of depression willing to receive antidepressant treatment in primary care, including those with comorbid physical or mental illness. Exclusion criteria: already taking antidepressants, pregnant, breast-feeding, terminal illness Open-label RCT, with partial preference design (following randomisation, treatment could be prescribed from a different class to the one allocated at random, if participants or their doctor preferred an alternative). (Peveler2005; N=327; entered preference group n=92; followed-up at 12 months n=171) Source of efficacy data: RCT (n=264 for depression-free weeks, n=262 for QALYs) Source of resource use data: RCT (n=324; sub-analysis included for those who provided	Costs: GP time (surgery contact, by telephone, home visit), other staff time (practice nurse, district nurse, CPN, counsellor, psychiatrist), day centre, non-psychiatric hospital clinic, A&E, psychiatric and non-psychiatric in-patient stay Mean total cost per person (95%CI): TCAs £762 (£553 to £1059) SSRIs £875 (£675 to £1355) LOF £867 (£634 to £1521) (p=0.09) Outcome measures: number of depression-free weeks (DFW, defined as a Hospital Anxiety and Depression Scale - Depression subscale (HADS-D) <8) and QALYs based on EQ-5D ratings (UK tariff) Number of depression-free weeks per person (95%CI): TCAs 25.3 (21.3 to 29.0) SSRIs 28.3 (24.3 to 32.2) LOF 24.6 (20.6 to 28.9) p=0.327 Mean QALYs per person, adjusted for baseline (95%CI): TCAs 0.548 (0.481 to 0.606)	ICERs SSRI vs. TCAs £59/DFW TCAs vs. LOF £183/DFW (TCAs extendedly dominated) SSRI vs. LOF £32/DFW SSRIs vs. LOF £5,686/QALY LOF vs. TCAs £23,250/QALY (LOF extendedly dominated) SSRIs vs. TCAs £2,692/QALY Probability of SSRIs being cost-effective approximately 0.6 at WTP of £20,000/QALY	Perspective: NHS Currency: UK£ Cost year: 2002 Time horizon: 12 months Discounting: NA Applicability: directly applicable Quality: minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		efficacy data, and used in estimation of ICERs/CEACs) Source of unit costs: national sources	SSRIs 0.586 (0.523 to 0.641) LOF 0.552 (0.493 to 0.612) p=562		

Table 42. Economic evidence table for exercise plus treatment as usual versus treatment as usual alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Chalder 2012 UK Cost-utility analysis	Interventions: Physical activity intervention delivered by a physical activity facilitator plus GP treatment as usual GP treatment as usual (TAU), which may include antidepressant medication, counselling or referral to secondary mental health services	Adults 18-69 years of age, with a recent first or new episode of mild/moderate depression (BDI score ≥14), who were not taking antidepressants at the time of assessment or had been prescribed antidepressants within 4 weeks of assessment but had had an antidepressant-free period of 4 weeks prior to that Pragmatic, multicentre RCT (N=361, excluded from clinical analysis due to high attrition rates) Source of efficacy and resource use data: RCT (at 12 months EQ-5D data n=195; complete resource use data n=156; multiple imputation used in sensitivity analysis)	Costs: intervention (physical activity facilitator's time), primary care professionals' time (GP, practice nurse, phlebotomist, health visitor, district nurse, midwife, nurse practitioner, mental health worker, counsellor, community psychiatric nurse, physiotherapist), paramedic, A&E, outpatient care, walk-in centre, NHS Direct out-of-hours care, medication, productivity losses Mean total service cost per person: Physical activity £ 646; TAU £350 Difference: £296 (95%CI £202 to £390) Primary outcome measure: QALYs estimated using EQ-5D ratings (UK tariff) QALYs per person: Physical activity: 0.809; TAU 0.795 Difference 0.014 (95%CI -0.033 to 0.061)	Under NHS & PSS perspective: Using completers' data: ICER of physical activity vs. TAU: £20,834/QALY Probability of physical activity being cost-effective at £20,000 and £30,000/QALY: 0.49 and 0.57, respectively Using imputed data: ICER of physical activity vs. TAU £19,394/QALY Probability of physical activity being cost-effective at £20,000 and £30,000/QALY: 0.50 and 0.60, respectively	Perspective: NHS & PSS (and societal) Currency: GBP£ Cost year: 2009 Time horizon: 12 months Discounting: NA Applicability: directly applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit costs: national sources			

Economic evidence tables for review question: For adults with a new episode of more severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 43. Economic evidence table for self-help with support: computerised cognitive behavioural therapy (CBT) with support added to treatment as usual versus treatment as usual alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Gilbody 2015/ Littlewood 2015 UK Cost-utility analysis	Interventions: Computerised, commercially produced CBT (Beating the Blues) with therapist support in addition to treatment as usual (cCBT1) Computerised, free to use cCBT (MoodGYM) with therapist support in addition to treatment as usual (cCBT2) Treatment as usual, comprising GP care with no constraints on the range of treatments that	Adults with symptoms of depression (PHQ-9 score ≥10) Pragmatic multicentre RCT (Gilbody2015 / Littlewood 2015, N=691) Source of efficacy and resource use data: RCT (EQ-5D data available for n=416 at 24 months; NHS cost data available for n=580) Source of unit costs: national sources	Costs: intervention (licence fee, cost of support), GP or nurse visits (including telephone call appointments), out-of-hours GP services, inpatient stays, outpatient visits, other community services (including counsellors, psychologists, psychiatrists, CMHT and IAPT services), depression-related medication (antidepressants, antipsychotics, mood stabilisers, sleeping tablets, anxiety medication) Mean total cost per person (SE): cCBT1: £1,186 (£80); cCBT2: £1,098 (£135); TAU: £1,121 (£62) Adjusted mean differences (95% CI) cCBT1 vs TAU: £104 (-£67 to £275) cCBT2 vs TAU: -£106 (-£262 to £50) Primary outcome measure: QALYs estimated based on EQ-5D (UK tariff) Number of QALYs per person (SE):	cCBT1 dominated by TAU TAU vs cCBT2 £6,933/QALY Probability of each intervention being cost effective at WTP £20,000/QALY: cCBT1: 0.038 cCBT2: 0.417 TAU: 0.545 Using SF-6D QALYs: cCBT1 dominated by TAU cCBT2 dominant Probability of each intervention being cost-effective at WTP £20,000/QALY: cCBT1: 0.007 cCBT2: 0.756 TAU: 0.237 Results robust to inclusion of depression-related costs only	Perspective: NHS & PSS Currency: GBP£ Cost year: 2012 Time horizon: 2 years Discounting: 3.5% annually Applicability: directly applicable Quality: minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	could be accessed (TAU)		cCBT1: 1.333 (0.034) cCBT2: 1.356 (0.033) TAU: 1.389 (0.033) Adjusted mean differences (95% CI) cCBT1 vs TAU: -0.044 (-0.117 to 0.030) cCBT2 vs TAU: -0.015 (-0.092 to 0.061)	and to consideration of completers' data only (instead of imputed data analysis) Little evidence of an interaction effect between preference and treatment allocation on outcomes	

Table 44. Economic evidence table for counselling versus antidepressants

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Miller 2003 UK Cost effectiveness analysis	Interventions: Generic psychological therapy comprising 6 weekly 50-minute sessions (counselling) Routinely prescribed antidepressant drugs, comprising dothiepin (150 mg) taken at night, fluoxetine (20 mg) taken once daily or lofepramine (140–210 mg) taken daily in divided doses, or a different drug if it was judged necessary by GP (AD)	Adults aged 18-70 years who met diagnostic criteria for major depression (assessed by their GP). Exclusion criteria: psychosis, suicidal tendencies, postnatal depression, recent bereavement, drug or alcohol misuse RCT (Bedi2000 /Chilvers 2001, N=103); people refusing randomisation but agreeing to participate in the patient preference trial were given the treatment of their choice (N=220) Source of efficacy data: RCT (at 12 months n=81) and preference trial (at 12 months n=163)	Costs: intervention (counselling, medication), depression-related GP visits, psychiatric inpatient & outpatient care Mean cost (SD) per person: RCT Counselling: £302 (£38) AD: £344 (£62); p=0.777 Preference trial: Counselling: £336 (£25) AD: £263 (£34) p =0.005 Primary outcome measure: global outcome, assessed by a psychiatrist blind to treatment allocation, using the research diagnostic criteria (RDC), BDI score and GP notes. The outcome was good if the person responded to treatment within 8 weeks and then remained well	RCT: ICER of AD vs. counselling £263/ extra person with a good global outcome Probability of counselling being cost-effective: 0.25 and 0.10 at a WTP of £500 and £2,000 per extra person with a good global outcome, respectively Sensitivity analysis: assuming missing data were good: probability of counselling being cost-effective increases for any WTP; assuming missing data were poor: probability of counselling being cost-	Perspective: NHS (only depression-related costs considered) Currency: UK£ Cost year:1995 Time horizon: 12 months Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of resource use data: RCT (at 12 months n=103) and preference trial (at 12 months n=215) Source of unit costs: national sources and local costs for counsellors	% of people with good global outcome: RCT Counselling: 25%, AD: 41%, p=0.196 Preference trial: Counselling: 36%, AD: 28%, p=0.191	effective slightly increases for WTP<£1,500 and decreases for WTP >£1,500. Preference trial: ICER of counselling vs. AD £912/ extra person with a good global outcome	

Table 45. Economic evidence tables for SSRIs: sertraline versus placebo

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Hollingworth 2020 UK Cost-utility analysis	Interventions: Sertraline Placebo	Adults aged 18-74 years presenting to primary care with depression or low mood during the past 2 years who had not received antidepressant or anti-anxiety medication in the previous 8 weeks. Pragmatic RCT (N=655) (Lewis 2019) Source of efficacy & resource use data: RCT, analysis based on data imputation. n=505 with utility (EQ-5D) data available; cost data available for n=381	Costs: sertraline, primary care consultations and phone calls (GP, nurse), medication, inpatient and outpatient care, accident and emergency, community care, home visits, other community care Mean imputed total cost /person (SD): Sertraline: £154 (£19) Placebo: £177 (£26) Difference: −£22 (−£87 to £42) Sub-group with mild depression: Difference: −£19 (−£154 to £116) Sub-group with moderate depression: Difference: £4 (−£145 to £152) Sub-group with severe depression: Difference: −£41 (−£109 to £27) Outcome measure: QALY estimated based on EQ-5D (UK tariff)	Imputed incremental net monetary benefit (95% CI) at WTP £20,000 /QALY: whole sample: £122 (£18 to £226) Sub-group with mild depression: £102 (−£114 to £317) Sub-group with moderate depression: £135 (−£69 to £339) Sub-group with severe depression: £131 (−£18 to £281) Probability of sertraline being cost-effective at WTP	Perspective: NHS & personal social services Currency: GBP£ Cost year: 2018 Time horizon: 12 weeks Discounting: NA Applicability: directly applicable Quality: minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit costs: national sources	Mean imputed QALYs / person (SD): Sertraline: 0.182 (0.002) Placebo: 0.177 (0.002) Difference: 0.005 (−0.003 to 0.012) Sub-group with mild depression: Difference: 0.004 (−0.004 to 0.012) Sub-group with moderate depression: Difference: 0.007 (0 to 0.014) Sub-group with severe depression: Difference: 0.005 (−0.002 to 0.011)	£20,000 /QALY: >95% in whole sample; >70% in each sub-group	

Table 46. Economic evidence tables for SSRIs: escitalopram versus citalopram

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Wade 2005b UK Cost effectiveness analysis	Interventions: Escitalopram Citalopram	Adults with major severe depression with baseline MADRS score ≥ 30 Decision-analytic modelling Source of efficacy data: published meta-analysis of RCTs Source of resource use data: published literature and expert opinion Source of unit costs: national sources	Costs: study medication, GP and psychiatrist visits, inpatient psychiatric hospitalizations, treatment discontinuation, treatment-emergent AEs, attempted suicide. Sick leave Mean (range) total NHS cost per person: Escitalopram: £422 (£404-£441) Citalopram £454 (£436-£471) Outcome measures: % of remission, defined as MADRS score ≤ 12, and % remission without switch % of remission: mean (range) Escitalopram: 53.7% (50.3%-57.5%) Citalopram: 48.7% (45.8%-51.7%) % of remission without switch: mean (range) Escitalopram: 41.7% (37.5 %-46.3%) Citalopram: 30.8% (27.5%-34.6%)	Escitalopram dominates citalopram Results robust to changes in drug-specific probabilities and cost data PSA: Escitalopram was dominant in >99.8% of iterations	Perspective: NHS (and societal) Currency: GBP£ Cost year: 2003 Time horizon: 26 weeks Discounting: NA Applicability: directly applicable Quality: potentially serious limitations

Table 47. Economic evidence tables for SSRIs versus SNRIs: escitalopram versus citalopram versus venlafaxine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Wade 2005a UK Cost effectiveness analysis	Interventions: Escitalopram Citalopram Venlafaxine	Adults with major depression with baseline MADRS score between 18-40 Decision-analytic modelling Source of efficacy data: meta-analysis of head-to-head RCTs between escitalopram and citalopram; and between escitalopram and venlafaxine Source of resource use data: General Practice Research Database, published literature and expert opinion Source of unit costs: national sources	Costs: study medication, staff time (GP, psychiatrist, hospitalisation, community services, attempted suicide; sick leave Mean (range) total NHS cost per person: Escitalopram: £465 (£436-£493) Citalopram: £544 (£514-£573) Escitalopram: £376 (£342-£410) Venlafaxine: £415 (£382-£449) Outcome measure: % of remission, defined as MADRS score ≤ 12 % of remission: mean (range) Escitalopram: 63.5% (61.5%-65.4%) Citalopram: 58.2% (56.3%-60.3%) Escitalopram: 68.9% (66.7%-70.9%) Venlafaxine: 68.5% (66.2%-70.6%)	Escitalopram dominates both citalopram and venlafaxine	Perspective: NHS (and societal) Currency: UK£ Cost year: 2003 Time horizon: 26 weeks Discounting: NA Applicability: directly applicable Quality: potentially serious limitations

Table 48. Economic evidence tables for SSRIs versus SNRIs: escitalopram versus duloxetine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Wade 2008 UK	Interventions: Escitalopram Duloxetine	Outpatients aged 18–65 years with moderate-to-severe	Costs: medication, staff time (GP, psychiatrist, cardiologist, ear-nose-throat specialist, gastroenterologist, dermatologist, psychologist, nurse, social worker, physiotherapist,	Escitalopram dominant across all outcomes	Perspective: NHS & sick leave

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Cost-effectiveness analysis		depression (baseline Montgomery-Aberg Depression Rating Scale [MADRS] total score ≥26 and a Clinical Global Impression Severity [CGI-S] score ≥4) and duration of current depressive episode of 12 weeks to 1 year International multi-centre RCT (N=295) (Wade 2007) Source of efficacy & resource use data: RCT, analysis based on data imputation; completers for economic analysis n=223 Source of unit costs: national sources	occupational therapist, alternative therapy), hospitalisation (psychiatry, emergency, general practice, surgery), sick leave Mean difference in healthcare costs (SD): -£145 (-£387 to -£42) Outcome measures: Sheehan Disability Scale score (SDS), MADRS score, response response (MADRS score decrease ≥50%) and remission (MADRS score ≤12) Mean difference in effects: MADRS change in total score 1.7 (-0.1 to 3.4) SDS change in total score 2.4 (0.4 to 4.1) Response probability 5.0% (-2.8% to 12.7%) Remission probability 3.3% (-5.7% to 11.8%)		Currency: GBP£ Cost year: 2006 Time horizon: 24 weeks Discounting: NA Applicability: directly applicable Quality: potentially serious limitations

Table 49. Economic evidence tables for SSRIs versus mirtazapine: paroxetine versus mirtazapine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Romeo 2004 UK Cost effectiveness analysis	Interventions: Mirtazapine 30–45 mg/day	Adults with major depression and baseline $HAMD_{17}$ score >18 treated in primary care RCT (N=197) (Wade2003)	Costs: medication, hospital inpatient stays and outpatient attendances, day care; contacts with GPs, community psychiatric nurses, social workers, opticians, physiotherapists and other specialists Mean total NHS cost per person: Mirtazapine: £1408 (SD (£1777)	Mirtazapine dominates paroxetine Results robust to changes in costs	Perspective: NHS and social care (and societal) Currency: UK£ Cost year: 2002

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	Paroxetine 20–30 mg/day	Source of efficacy & resource use data: RCT (data available for economic analysis n=177) Source of unit costs: national sources	Paroxetine: £1528 (SD £2022) Mean difference -£120 (95%CI -£750 to £377, p=0.51) Outcome measure: % of response defined as at least 50% decrease in $HAMD_{17}$; changes in Quality of Life in Depression Scale (QLDS) from baseline to endpoint % of response: Mirtazapine: 63% Paroxetine: 56% (p=0.31) Change in QLDS Mirtazapine: 13 Paroxetine: 9 (p=0.021, favouring mirtazapine)	Probability of mirtazapine being cost-effective 80% and 89%, at WTP zero and £1000 for a point improvement in $HAMD_{17}$	Time horizon: 24 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 50. Economic evidence tables for SSRIs versus SNRIs versus mirtazapine: SSRIs versus duloxetine versus venlafaxine versus mirtazapine

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Benedict 2010 UK Cost-utility analysis	Interventions: Duloxetine SSRIs Venlafaxine Mirtazapine	Adults with moderate to severe major depression defined by a $HAMD_{17}$ score ≥19, having a new treatment episode in primary care Decision-analytic modelling Source of efficacy data: meta-analyses of clinical trials -randomisation likely broken	Costs: medication, A&E Visits, GPs, psychiatrists, hospitalisation Mean total cost per person: Duloxetine £543 SSRIs £486 Venlafaxine £585 Mirtazapine £516 Outcome measure: QALY estimated based on EQ-5D ratings (UK tariff) Number of QALYs per person:	Duloxetine dominant over venlafaxine. SSRIs dominant over mirtazapine ICER of duloxetine versus SSRIs: £6,304/QALY Probability of duloxetine being cost-effective at WTP £20,000/QALY: approximately 70% Results sensitive to changes in efficacy (response / relapse) and utility values	Perspective: Scottish NHS Currency: UK£ Cost year: likely 2003 Time horizon: 48 weeks Discounting: NA Applicability: directly applicable Quality: potentially

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of resource use data: expert opinion Source of unit costs: national sources	Duloxetine 0.665 SSRIs 0.656 Venlafaxine 0.663 Mirtazapine 0.654		serious limitations

Table 51. Economic evidence tables for SSRIs versus SNRIs versus TCAs: fluoxetine versus venlafaxine versus amitriptyline

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Lenox-Smith 2009 UK Cost-utility analysis	Interventions: Venlafaxine Fluoxetine Amitriptyline	Adult outpatients with major depression Decision-analytic modelling Source of efficacy data: pooled data from meta-analysis; a single RCT for amitriptyline vs. venlafaxine Source of resource use data: Delphi panel Source of unit costs: national sources	Costs: medication, lab testing, clinical examinations, community psychiatric nursing, inpatient and outpatient services, staff time (GP, psychiatrist, psychologist), psychotherapy Mean total cost per person: Venlafaxine £1530 Fluoxetine £1539 Amitriptyline £1558 Outcome measure: QALY estimated based on the presumed utilities of a depression-free day and a severely depressed day Mean QALYs per person Venlafaxine 0.098 Fluoxetine 0.090 Amitriptyline 0.085	Venlafaxine dominates fluoxetine and amitriptyline Results robust to changes in costs. Results sensitive to the value of the utility gain associated with a depression-free day	Perspective: NHS Currency: UK£ Cost year: 2006 Time horizon: 24 weeks Discounting: NA Applicability: partially applicable Quality: potentially serious limitations

Table 52. Economic evidence table for combined CBT & antidepressant (fluoxetine) versus antidepressant alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Simon 2006 UK Cost effectiveness and cost-utility analysis	Interventions: Combination therapy comprising 16 sessions of CBT lasting 50min each and antidepressant therapy (fluoxetine) (Combo) Antidepressant therapy alone, comprising fluoxetine 40mg daily for 3 months and standard outpatient care (AD)	Adults with moderate depression and adults with severe depression Decision-analytic modelling (decision tree) Source of efficacy data: systematic literature review & meta-analysis of RCTs Source of resource use data: published literature and expert opinion Source of unit costs: national sources	Costs: intervention (clinical psychologist's time for CBT, antidepressant medication, dispensing fee, outpatient care with consultant psychiatrist or specialist registrar), subsequent depression treatment over 12months Mean total cost per person: Combo £1,297; AD £660; difference £637 Outcome measures: Probability of successful treatment (remission and no relapse over 12 months) with remission defined as HRSD-17 ≤ 6 or HRSD-24 ≤ 8 QALYs estimated based on vignettes valued by service users using SG Outcome results: Probability of successful treatment: Combo 0.29; AD 0.14; difference 0.16 QALYs per person with severe depression: Combo 0.63; AD: 0.52; difference 0.11 QALYs per person with moderate depression Combo 0.89; AD 0.84; difference 0.04	ICER of Combo vs AD: £4,056 per additional successfully treated person (95% CI £1,400 to £18,300) Moderate depression: £14,540/QALY (95%CI £4,800 to £79,400/QALY) Probability of Combo being cost-effective at WTP £30,000/QALY 0.88 Severe depression: £5,777/QALY (95% CI £1,900 to £33,800/QALY) Probability of Combo being cost-effective at WTP £30,000/QALY 0.97 Results sensitive to changes in relative efficacy (in terms of remission, relapse)	Perspective: NHS Currency: GBP£ Cost year: 2003 Time horizon: 15 months Discounting: NA Applicability: partially applicable Quality: minor limitations

Table 53. Economic evidence table for combined CBT & antidepressant (citalopram) versus CBT alone versus antidepressant alone

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Koeser 2015 UK	Interventions: Antidepressant therapy alone,	Adults with moderate or severe major depression	Costs: intervention (clinical psychologist's time for CBT, antidepressant medication,	Combo dominated by CBT	Perspective: NHS Currency: GBP£

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Cost-utility analysis	comprising citalopram 20mg daily for 15 months and standard outpatient care (AD) Cognitive Behavioural Therapy (CBT) comprising 16 acute + 2 booster sessions for responders, each lasting 50 min Combination therapy comprising CBT and AD treatment (Combo)	Decision-analytic modelling (decision tree) Source of efficacy data: systematic screening of database containing RCTs that compare psychological treatments (single or combined) for adults with depression with a control intervention; NMA Source of resource use data: published literature that reported expert opinion and analysis of RCT data Source of unit costs: national sources	dispensing fee, outpatient care with consultant psychiatrist or specialist registrar), service use associated with remission, response, no response Mean total cost per person: AD: £3,645; CBT: £4,418 Combo: £5,060 Outcome measures: QALYs estimated based on EQ-5D (UK tariff) Mean total QALYs per person: AD: 1.236; CBT: 1.274 Combo: 1.274	ICER of CBT vs AD: £20,039/QALY Probability of being best at WTP £25,000/QALY: CBT: 0.43 AD: 0.37 Combo: 0.20 Results sensitive to changes in inclusion criteria for RCTs for acute and follow-up treatment and to use of SF-6D values	Cost year: 2012 Time horizon: 27 months Discounting: 3.5% annually Applicability: directly applicable Quality: minor limitations

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: For adults with a new episode of less severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 54. Economic evidence profile for individual problem solving versus treatment as usual

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Kendrick 2005/2006a UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	£483	-0.02	Problem solving dominated by TAU	Significant difference in costs; non-significant difference in effects; majority of bootstrapped iterations showed problem solving being dominated by TAU

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment as usual
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 26 weeks; analysis conducted alongside RCT (N=247; analysis based on n=184 with clinical data available; cost data available for n=159); national unit costs used; statistical analyses conducted; cost effectiveness planes presented.
3. UK study; NHS perspective; QALY estimates based on EQ-5D (UK tariff)

Table 55. Economic evidence profile for computerised CBT (with minimal support) versus treatment as usual

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Kaltenthaler 2006 UK	Potentially serious limitations[2]	Directly applicable[3]	Outcome: QALY 3 commercially produced computerised CBT packages assessed	From £95 to £287 (depending on package)	From 0.01 to 0.08 (depending on package)	From £2,678 to £10,614 (depending on package)	Probability of cCBT being cost-effective at WTP £44,600/QALY: 0.54-0.87 (depending on package)

cCBT: computerised cognitive behavioural therapy; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 18 months; analysis based on decision-analytic economic modelling; efficacy data based on analysis of individual-level RCT data, published RCT data and further assumptions; resource use data based on manufacturer submissions, published data and other assumptions; manufacturer prices used for intervention, national unit costs used for other cost elements; sensitivity analyses, including PSA conducted; CEACs presented
3. UK study; NHS perspective; QALY estimated based on EQ-5D ratings (UK tariff)

Table 56. Economic evidence profile for sertraline versus placebo

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Hollingworth 2020 UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	Total sample: −£23 (−£91 to £44) Mild depression: −£20 (−£161 to £121)	Total sample: 0.005 (−0.003 to 0.012) Mild depression: 0.004 (−0.004 to 0.012)	Total sample: Sertraline dominant Mild depression: sertraline dominant	Probability of sertraline being cost-effective at WTP £20,000/QALY : >0.95 in total sample; >0.70 in mild depression

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 weeks; analysis conducted alongside RCT (N=655; utility data available for n=505; cost data available for n=381); national unit costs used; imputation of missing data undertaken; statistical analyses including PSA conducted; cost effectiveness acceptability curve presented.
3. UK study; NHS & personal social services perspective; QALY estimates based on EQ-5D (UK tariff)

Table 57. Economic evidence profile for SSRIs added to GP supportive care compared with GP supportive care alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER	Uncertainty
Kendrick 2009 UK	Minor limitations[2]	Directly applicable[3]	Outcomes: HAMD17 and QALY	12 weeks -£36 26 weeks £195	12 weeks -2.49 0.005 26 weeks -1.81 0.010	12 weeks: SSRIs & supportive care dominant 26 weeks: £115/HAMD17 reduction in score £18,894/QALY	Probability of SSRI plus supportive care being cost-effective >0.50 at WTP £102/HAMD17 unit reduction; 0.65-0.70 at WTP £20,000-£30,000 /QALY

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 and 26 weeks; analysis conducted alongside RCT (N=220; 12-week completers n=196; 6-month follow-up n=160); national unit costs used; statistical analyses (including bootstrapping) conducted; CEACs presented.
3. UK study; NHS and social care perspective; QALY estimates based on SF-36/SF-6D (UK tariff)

Table 58. Economic evidence profile for SSRIs versus TCAs versus lofepramine

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER	Uncertainty
Peveler 2005/ Kendrick 2006b UK	Minor limitations[2]	Directly applicable[3]	Outcomes: number of DFWs, defined as a HADS-D score <8; QALY	Versus lofepramine: TCAs: -£162 SSRIs: £12	Versus lofepramine: DFWs: TCAs: 0.7 SSRIs: 3.7 QALYs: TCAs: -0.004 SSRIs: 0.034	SSRIs vs lofepramine £49/DFW (TCAs extendedly dominated) SSRIs vs TCAs £4,142/QALY (lofepramine extendedly dominated)	Probability of SSRIs being cost-effective 0.6 at WTP £20,000/QALY

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 months; analysis conducted alongside an open label RCT (N=327; entered preference group n=92; followed-up at 12 months n=171); national unit costs used; statistical analyses (including bootstrapping) conducted; CEACs presented.
3. UK study; NHS perspective; QALY estimates based on EQ-5D ratings (UK tariff)

Table 59. Economic evidence profile for exercise plus treatment as usual versus treatment as usual alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER	Uncertainty
Chalder 2012 UK	Potentially serious limitations[2]	Directly applicable[3]	Outcome: QALY	£352	0.014	£24,793	Probability of cost effectiveness at £20,000 and £30,000/QALY: 0.49 and 0.57, respectively Using imputed data: ICER £23,079/QALY Probability of cost effectiveness at £20,000 and £30,000/QALY: 0.50 and 0.60, respectively

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 months; analysis conducted alongside RCT (N=361; at 12 months EQ-5D data n=195; complete resource use data n=156); national unit costs used; statistical analyses conducted, including bootstrapping; PSA undertaken and CEACs presented; one way sensitivity analysis undertaken
3. UK study; NHS & PSS perspective; QALY estimates based on EQ-5D (UK tariff)

Table 60. Economic evidence profile for various pharmacological, psychological and physical interventions

Study and country	Limitations	Applicability	Other comments	Incremental cost / 1000 people (£)[1]	Incremental effect / 1000 people	NMB (£) per person[1]	Uncertainty
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY	Versus GP care: Sertraline 68,564 Lofepramine 225,008 cCBT -32,327 cCBT with support 24,466 BA individual 482,191 BA group 113,499 CBT individual 468,144 CBT group 60,259 Individual problem solving 77,470 Non-directive counselling 559,495 IPT 478,353 Short-term PDPT 883,503 MBCT group 234,268 Exercise individual 816,427 Exercise group 28,712	Versus GP care: Sertraline 30.92 Lofepramine 31.35 cCBT 21.24 cCBT with support 21.24 BA individual 42.25 BA group 43.24 CBT individual 42.66 CBT group 54.50 Individual problem solving 6.75 Non-directive counselling 22.93 IPT 24.54 Short-term PDPT 37.18 MBCT group 36.70 Exercise individual 30.69 Exercise group 32.98	CBT group 32,900 BA group 32,622 Exercise group 32,501 Sertraline 32,420 MBCT group 32,370 cCBT 32,328 Lofepramine 32,272 cCBT with support 32,271 CBT individual 32,255 BA individual 32,233 Problem solving 31,928 IPT 31,883 GP care 31,871 Counselling 31,770 Short-term PDPT 31,731 Exercise individual 31,668	Probability of cost effectiveness at WTP £20,000/ QALY: CBT group 0.60 Results of pharmacological interventions sensitive to the risk of side effects

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy; QALY: quality-adjusted life year; WTP: willingness to pay

1. Costs expressed in 2020 British pounds.

2. Decision-analytic hybrid model, time horizon 12 weeks + 2 years; relative effects based on guideline systematic review and NMA; baseline effects derived from review of naturalistic studies; resource use based on published data supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented

3. UK study; NHS & PSS perspective; QALY estimates based on EQ-5D (UK tariff)

Economic evidence profiles for review question: For adults with a new episode of more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 61. Economic evidence profile for computerised cognitive behavioural therapy (CBT) with support versus treatment as usual

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Gilbody 2015 / Littlewood 2015 UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY 2 computerised CBT programmes assessed: one commercially produced (cCBT1), the other freely available (cCBT2)	£117 -£119 (depending on package)	-0.044 -0.015 (depending on package)	cCBT1 dominated cCBT2 less costly, less effective £7,798	Probability of each intervention being cost effective at WTP £20,000/QALY: cCBT1 0.038; cCBT2 0.417; TAU: 0.545 Using SF-6D QALYs: cCBT1 dominated by TAU; cCBT2 dominant Probability of each intervention being cost-effective at WTP £20,000/QALY: cCBT1 0.007; cCBT2 0.756; TAU: 0.237 Results robust to inclusion of depression-related costs only and to consideration of completers' data only (instead of imputed data analysis) Little evidence of an interaction effect between preference and treatment allocation on outcomes

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 2 years; analysis conducted alongside RCT (N=691; at 24 months EQ-5D data available for n=416 and NHS cost data available for n=580); national unit costs used; statistical analyses including regression analysis to control for covariates conducted; Cholesky decomposition conducted to account for covariance in costs and QALYs; CEACs presented; deterministic sensitivity analysis conducted
3. UK study; NHS & PSS perspective; QALY estimated based on EQ-5D ratings (UK tariff)

Table 62. Economic evidence profile for counselling versus antidepressants

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Miller 2003 UK	Potentially serious limitations[2]	Partially applicable[3]	Outcome: % of people with good 'global outcome', reflecting response to treatment within 8 weeks and remaining well	RCT: -£83 Preference trial: £145	RCT: -16% Preference trial: 8%	RCT: AD vs counselling £524 Preference trial: counselling vs AD £1,816	RCT: probability of counselling being cost-effective 0.25 and 0.10 at WTP £995 and £3,983/extra person with good global outcome, respectively Assuming missing data reflected good outcomes, probability of counselling being cost-effective increased at any WTP Assuming missing data represented poor outcomes, probability of counselling being cost-effective slightly increased for WTP < £2,755 /good global outcome and decreased for WTP> £2,755 /good global outcome

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 months; analysis conducted alongside RCT (N=103, at 12 months efficacy data for n=81 and resource data for n=103) and preference trial (N=220; at 12 months efficacy data for n=163 and resource use data n=215); only depression-related costs considered; national unit costs used except for counsellors, where local costs were used; statistical analyses conducted including bootstrapping, CEACs presented.
3. UK study; NHS perspective; QALY not used as an outcome 3. UK study; NHS & PSS perspective; QALY estimated based on EQ-5D ratings (UK tariff)

Table 63. Economic evidence profile for sertraline versus placebo

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Hollingworth 2020 UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY Subgroup analysis by	Moderate depression: £4 (−£152 to £159) Severe depression: −£43 (−£114 to £28)	Moderate depression: 0.007 (0 to 0.014) Severe depression:	Moderate depression: £597/QALY	Probability of sertraline being cost-effective at WTP £20,000/QALY:

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
			severity level conducted		0.005 (−0.002 to 0.011)	Severe depression: sertraline dominant	>0.70 in each level of severity

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness to pay
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 12 weeks; analysis conducted alongside RCT (N=655; utility data available for n=505; cost data available for n=381); national unit costs used; imputation of missing data undertaken; statistical analyses including PSA conducted; cost effectiveness acceptability curve presented.
3. UK study; NHS & personal social services perspective; QALY estimates based on EQ-5D (UK tariff)

Table 64. Economic evidence profile for escitalopram versus citalopram

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Wade 2005b UK	Potentially serious limitations[2]	Directly applicable[3]	Population: adults with severe depression • Outcome: % of remission	-£48	5%	Escitalopram dominant	Results robust to changes in drug-specific probabilities and cost data PSA: Escitalopram dominant in >99.8% of iterations

ICER: incremental cost effectiveness ratio
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. UK study; NHS perspective; QALY not used as an outcome but intervention dominant (so no further judgements on cost effectiveness required)
3. Time horizon 26 weeks; analysis based on economic modelling, efficacy data from pooled RCTs; resource use data based on a general practice database, expert opinion and published studies; national unit costs used; statistical analyses conducted including PSA, funded by industry.SSRIs versus SNRIs

Table 65. Economic evidence profile for escitalopram versus citalopram versus venlafaxine

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Wade 2005a UK	Potentially serious limitations[2]	Directly applicable[3]	Population: adults with moderate-to-	Escitalopram: -£117 versus citalopram	Escitalopram: 5.3% versus citalopram	Escitalopram dominant	Results robust under different scenarios (changes

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
			severe depression • Outcome: % of remission	-£57 versus venlafaxine	0.4% versus venlafaxine		in rates of remission, relapse, discontinuation, unit costs)

ICER: incremental cost effectiveness ratio
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 26 weeks; analysis based on economic modelling, efficacy data from pooled RCTs; resource use data based on a general practice database, expert opinion and published studies; national unit costs used; statistical analyses conducted including PSA, funded by industry, side effects not considered in estimation of costs
3. UK study; NHS perspective; QALY not used as an outcome but intervention dominant (so no further judgements on cost effectiveness required)

Table 66. Economic evidence profile for escitalopram versus duloxetine

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Wade 2008 UK	Potentially serious limitations[2]	Directly applicable[3]	Outcomes: • SAS change in score • MADRS change in score • Response • Remission	Total sample: −£191 (−£510 to -£55)	2.4 (0.4 to 4.1) 1.7 (-0.1 to 3.4) 5.0% (-2.8% to 12.7%) 3.3% (-5.7% to 11.8%)	Escitalopram dominant	Difference in costs and SAS change in score statistically significant

ICER: incremental cost effectiveness ratio; MADRS: Montgomery-Asberg Depression Rating Scale; SAS: Sheehan Disability Scale
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. UK study; NHS perspective; no QALY used but intervention dominant
3. Time horizon 24 weeks; analysis conducted alongside RCT (N=295; health economic data for n=223); national unit costs used; imputation of missing data undertaken; no probabilistic sensitivity analysis conducted; cost effectiveness acceptability curves not presented.

Table 67. Economic evidence profile for paroxetine versus mirtazapine

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Romeo 2004 UK	Potentially serious limitations[2]	Directly applicable[3]	Outcomes: • Response	£185 (-£580 to £1,154)	7% -4	Paroxetine dominated by mirtazapine	Probability of mirtazapine being cost-effective 80% and 89%, at WTP zero

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
			• Change in QLDS				and £1000 for a point improvement in HAMD17 Results robust to changes in costs

HAMD: Hamilton Depression rating scale; ICER: incremental cost effectiveness ratio; QLDS: Quality of Life in Depression Scale
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. UK study; NHS perspective; no QALY used but intervention dominated
3. Time horizon 24 weeks; analysis conducted alongside RCT (N=197; health economic data for n=177); national unit costs used; imputation of missing data undertaken; probabilistic sensitivity analysis conducted; cost effectiveness acceptability curves presented; potential conflicts of interest as study funded by industry

Table 68. Economic evidence profile for SSRIs versus duloxetine versus venlafaxine versus mirtazapine

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Benedict 2010 UK	Potentially serious limitations[2]	Directly applicable[3]	• Outcome: QALY	Duloxetine versus: SSRIs: £88 Venlafaxine: -£65 Mirtazapine £42	Duloxetine versus: SSRIs 0.009 Venlafaxine 0.002 Mirtazapine 0.011	Duloxetine dominant over venlafaxine. SSRIs dominant over mirtazapine ICER of duloxetine versus SSRIs: £9,700/QALY	Probability of duloxetine being cost-effective at WTP £20,000/QALY: approximately 70% Results sensitive to changes in efficacy (response / relapse) and utility values.

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 48 weeks; analysis based on decision-analytic modelling; efficacy data derived from meta-analyses of clinical trials with randomisation possibly broken; disutility and costs due to side effects not considered; resource use estimates based on expert opinion; national unit costs used; funded by industry
3. UK study; Scottish NHS perspective; QALYs based on EQ-5D (UK tariff)

Table 69. Economic evidence profile for fluoxetine versus venlafaxine versus amitriptyline

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Lenox-Smith 2009 UK	Very serious limitations[2]	Partially applicable[3]	Outcome: QALY	Venlafaxine versus: Fluoxetine -£12 Amitriptyline -£37	Venlafaxine versus: Fluoxetine 0.008 Amitriptyline 0.013	Venlafaxine dominant	Results robust to changes in costs. Results sensitive to the value of the utility gain associated with a depression-free day

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 24 weeks; analysis based on decision-analytic modelling; method of synthesis of efficacy data unclear, but randomisation likely broken; disutility and costs due to side effects not considered; resource use estimates based on expert opinion; national unit costs used; funded by industry
3. UK study; NHS perspective; QALYs estimated based on the presumed utilities of a depression-free day and a severely depressed day

Table 70. Economic evidence profile for combined CBT and antidepressant versus antidepressant alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Simon 2006 UK	Minor limitations[2]	Partially applicable[3]	Population: adults with moderate or severe depression Outcomes: • % of successful treatment (remission and no relapse over 12 months) • QALY	£947	% successful treatment: 16% QALYs - moderate depression 0.04 - severe depression 0.11	£6,031/ successfully treated person £21,617/QALY for moderate depression £8,589/QALY for severe depression	95% CIs: £2,081 to £27,209/successsfully treated person £7,136 to £118,054/QALY for moderate depression £2,825 to 483,873/QALY for severe depression Results sensitive to changes in relative efficacy (remission, relapse). Probability of Combo being cost-effective at WTP £44,000/QALY: 0.88 for moderate depression and 0.97 for severe depression

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).

2. Time horizon 18 months; analysis based on economic modelling, efficacy data from systematic review and meta-analysis; resource use data based on expert opinion and published studies; national unit costs used; PSA conducted, CEACs presented; side effects not considered in estimation of costs or QALYs
3. UK study; NHS perspective; QALYs generated based on vignettes valued by service users using standard gamble techniques

Table 71. Economic evidence profile for combined CBT and antidepressant versus CBT alone versus antidepressant alone

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Koeser 2015 UK	Minor limitations[2]	Directly applicable[3]	Population: adults with moderate or severe depression Outcome: QALY	Vs citalopram: CBT £869 Combo £1,591	Vs citalopram: CBT 0.038 Combo 0.038	Combo dominated by CBT CBT vs citalopram: £22,538	Probability of CBT, citalopram, Combo being cost-effective at WTP £28,000/QALY: 0.43, 0.37 and 0.20, respectively Results sensitive to changes in inclusion criteria for RCTs for acute and follow-up treatment Using SF-6D values: ICER of CBT vs citalopram £36,646/QALY

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year
1. Costs uplifted to 2020 UK pounds using the NHS cost inflation index (Curtis 2020).
2. Time horizon 27 months; analysis based on economic modelling, efficacy data from systematic review and network meta-analysis; resource use data based on published estimates of expert opinion and analysis of RCT data; PSA conducted, CEACs presented; side effects not considered in estimation of costs or QALYs
3. UK study; NHS perspective; QALYs generated based EQ-5D ratings (UK tariff)

Table 72. Economic evidence profile for various pharmacological, psychological, physical and combined interventions

Study and country	Limitations	Applicability	Other comments	Incremental cost / 1000 people (£)[1]	Incremental effect / 1000 people	NMB (£) per person[1]	Uncertainty
Guideline economic analysis UK	Minor limitations[2]	Directly applicable[3]	Outcome: QALY Bias-adjusted analysis, using discontinuation and response in completers data after adjusting for bias due to small study size	Versus GP care: Escitalopram 117,987 Lofepramine 324,417 Duloxetine 131,915 Mirtazapine 115,955 Trazodone 134,755 cCBT 182,164 cCBT with support 202,467 BA individual 998,237 CBT individual 1,289,809 CBT group 437,628 Problem solving 196,894 Counselling 1,022,415 IPT 1,414,450 Short-term PDPT 1,247,280 Exercise individual 1,078,612 Exercise group 297,122 Acupuncture 826,761 CBT individual + escitalopram 1,307,809 Acupuncture + escitalopram 760,064	Versus GP care: Escitalopram 49.82 Lofepramine 57.26 Duloxetine 58.76 Mirtazapine 53.61 Trazodone 38.68 cCBT 5.57 cCBT with support 41.13 BA individual 94.92 CBT individual 86.57 CBT group 26.07 Problem solving 112.90 Counselling 54.43 IPT 56.06 Short-term PDPT 46.66 Exercise individual 35.72 Exercise group 56.57 Acupuncture -14.17 CBT individual + escitalopram 119.35 Acupuncture + escitalopram 81.34	Individual problem solving 28,929 CBT individual + escitalopram 27,947 Duloxetine 27,911 Mirtazapine 27,824 BA individual 27,768 Escitalopram 27,746 Acupuncture + escitalopram 27,735 Exercise group 27,702 Lofepramine 27,689 Trazodone 27,507 cCBT with support 27,488 CBT individual 27,309 CBT group 26,952 Counselling 26,934 GP care 26,868 cCBT 26,797 IPT 26,575 Short-term PDPT 26,554 Exercise individual 26,504 Acupuncture 25,758	Probability of cost effectiveness at WTP £20,000/ QALY: individual problem solving 0.71 Results of individual psychological interventions sensitive to the utility gains after remission; results of pharmacological and combined interventions sensitive to the risk of side effects from antidepressants

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy; QALY: quality-adjusted life year; WTP: willingness to pay

1. Costs expressed in 2020 British pounds.
2. Decision-analytic hybrid model, time horizon 12 weeks + 2 years; relative effects based on guideline systematic review and NMA; baseline effects derived from review of naturalistic studies; resource use based on published data supplemented by most up-to-date resource use and unit cost data; national unit prices used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALY estimates based on EQ-5D (UK tariff)

Appendix J – Economic analysis

Economic analysis for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Introduction – objective of economic modelling

The choice of initial treatment for adults with a new depressive episode was identified by the committee and the guideline health economist as an area with potentially major resource implications. Although existing economic evidence in this area is quite extensive, no study has currently assessed the relative cost effectiveness of the whole range of available interventions for adults with a new episode of depression in the UK. An economic model was therefore developed to assess the relative cost effectiveness of effective pharmacological, psychological, physical and combined interventions for the treatment of adults with a new episode of depression in the UK. Network meta-analyses (NMAs) were conducted to synthesise available evidence and inform the economic model.

The purpose of the economic model was to assess the best approach for treatment of a new episode of depression up to its (potential) resolution; the model included a two-year follow-up period, in order to incorporate cost-effective maintenance therapy aiming at preventing relapse, where appropriate, in people who remitted following acute treatment. However, people with depression may experience multiple recurrent episodes in the future, following treatment of the new episode, which have not been incorporated in the acute treatment model structure. The consequences (costs and impact on health-related quality of life [HRQoL]) of recurrent depressive episodes in the longer term have been considered in a separate model that was developed to assess the cost effectiveness of interventions for depression aiming at preventing relapse in adults with depression that is in remission. The economic analysis of interventions for relapse prevention is described in Evidence report C, appendix J.

Economic modelling methods

Population

The study population of the economic model comprised adults with depression initiating treatment for a new episode in primary care. This was decided because the majority of adults with a new episode of depression are treated in primary care in routine UK practice. Two populations were considered: adults with a new episode of less severe depression and adults with a new episode of more severe depression. The definition of less severe and more severe depression was the same as that used to classify RCTs in the two respective NMAs undertaken to estimate the acceptability and effectiveness of interventions for the treatment of a new episode of depression, which informed the economic analysis. The definition of less severe and more severe depression is provided in the review protocol shown in appendix A. Generally, according to the criteria used to classify RCTs, less severe depression corresponds to subthreshold and mild depression, while more severe depression corresponds to moderate and severe depression. The study population had no physical comorbidities, psychotic symptoms, complex or chronic depressive symptoms in accordance with the inclusion criteria of the systematic review of RCTs that informed the NMAs.

People in the economic analysis were assumed to be experiencing their first depressive episode if they had less severe depression and their third depressive episode if they had more severe depression, to cover a range of presentations of adults with a new episode of depression in routine clinical practice. The number of previous episodes determined the

study population's risk of relapse following remission of the current episode but had no impact on the effectiveness of interventions in treating their current episode.

The age of the cohorts considered in the economic model was determined by the mean age of onset of depression in adults and the number of the current new episode for which treatment was received.

Kessler 2005 reported the results of a national comorbidity household survey in the US, according to which the median age-of-onset of depression was 32 years (interquartile range 19-44 years). In a Swedish longitudinal cohort study of 3,563 people followed up for 30-49 years, the median age at first onset of depression was reported to be around 35 years (Mattisson 2007). A large (n=20,198) Scottish family-based population study designed to identify the genetic determinants of common diseases, including major depression disorder, reported a mean age of onset of major depressive disorder of 31.7 years (SD 12.3 years) among 2,726 participants that met DSM-IV criteria for current and/or past major depression disorder (Fernandez 2015). On the other hand, Andrade 2003 did a review of results of community epidemiological surveys on major depressive episodes that were carried out in 10 countries in America, Europe and Asia (the UK was not included in these countries); the authors reported a median age of onset of major depression in the early to mid-twenties in all countries other than Japan (late twenties) and the Czech Republic (early thirties). Based on this evidence and following committee's expert advice, the age of onset of major depression in the study population was set at 32 years.

According to the committee's expert opinion, the mean interval between 2 consecutive depressive episodes in people who experience relapses is about 2 years. Therefore, for modelling purposes, adults with a new episode of less severe depression were assumed to be 32 years of age (as this was their first episode) and adults with more severe depression were assumed to be 36 years of age (as this was their third episode).

The percentage of women in each cohort were estimated to be 56%, based on weighted epidemiological data on depressive episodes reported in the most recent adult psychiatric morbidity household survey conducted in England (McManus 2016).

Determining the age and gender mix of the cohorts was necessary in order to estimate mortality risks in the model.

Interventions assessed

The range of interventions assessed in the economic analysis was determined by the availability of relevant clinical data synthesised in the NMA. The selection of classes of interventions was made based on the following criteria:

- The economic analysis on each population (adults with less severe depression and adults with more severe depression) assessed only classes of interventions that were included in the respective (in terms of study population) NMAs.

For each population, only classes of interventions that had been tested on at least 50 participants (across RCTs) in the NMA of standardised mean difference (SMD), which was the main clinical outcome, as well as in the NMAs of discontinuation (for any reason), response in completers and remission in completers (relevant only to the analysis of treatments for more severe depression) were included in the economic analysis, as these outcomes were essential in order to populate the economic model. This followed the committee's decision to consider only treatment classes that had been tested on at least 50 participants across the RCTs included in the respective NMA, after looking at the total size of the evidence base on treatments for a new episode of less severe depression and the large volume of evidence for some treatment classes relative to others.

- The NMA outcomes considered in the economic analysis are described in the 'Summary of methods', under 'Evidence Synthesis'. An exception to this rule was made for classes of interventions that are routinely available in the NHS, that is, such classes were included

in the analysis even if they had been tested on fewer than 50 participants in the NMAs mentioned above. For some treatment classes, inclusion in the economic model was not possible as no data were available on one or more NMA outcomes that informed economic modelling. For such classes, additional relevant data were sought by contacting authors of studies already included in the guideline systematic review, so as to enable inclusion of the classes in the respective NMAs and, subsequently, in the economic modelling.

- In addition, only classes with a higher mean effect on the SMD outcome compared with the selected reference treatment (treatment as usual [TAU] in less severe depression and placebo in more severe depression) were considered in the economic analysis.

Once the classes of interventions for inclusion in the economic analysis were determined, one intervention was used as exemplar within each class, so that the model utilised individual intervention (rather than class) effects and costs. The selection of interventions from each class was based on judgement, using a number of criteria:

- the size (volume) of the evidence base for each intervention
- the availability of interventions within the NHS: more commonly used interventions had a priority over less commonly used interventions
- their relative effectiveness: interventions with higher effects within a class were better candidates for selection
- the side-effect profile in the case of pharmacological treatments.

In addition to active interventions, the economic model also considered non-specific GP care as a benchmark treatment option, which, in terms of effectiveness, was reflected in RCT arms informing the reference treatment (TAU arms for less severe depression and placebo arms for more severe depression). GP care was considered as an option for both study populations. Based on the above criteria, the following interventions were included in the economic analysis for each study population [in brackets the classes they belong to]:

<u>Adults with less severe depression</u>

- pharmacological interventions
  - sertraline [selective serotonin reuptake inhibitors (SSRIs)]
  - lofepramine [tricyclic antidepressants (TCAs)]
- psychological interventions
  - computerised cognitive behavioural therapy (cCBT) without or with minimal support [self-help without or with minimal support]
  - cCBT with support [self-help with support]
  - individual behavioural activation (BA) [individual behavioural therapies (BT)]
  - group BA [group BT]
  - individual CBT (under 15 sessions) [individual cognitive therapy (CT)/CBT]
  - group CBT (under 15 sessions) [group CT/CBT]
  - individual problem solving [individual problem solving]
  - non-directive/supportive/person-centred counselling [individual counselling]
  - individual interpersonal psychotherapy (IPT) [individual IPT];
  - individual short-term psychodynamic psychotherapy (PDPT) [individual short-term PDPT]
  - group mindfulness-based cognitive therapy (MBCT) [mindfulness or meditation group]
- physical interventions
  - supervised high intensity individual exercise [individual exercise]
  - supervised high intensity group exercise [group exercise]

- GP care, reflected in the RCT arms of the reference treatment for less severe depression [TAU]

Adults with more severe depression

- pharmacological interventions
  - escitalopram [SSRIs]
  - lofepramine [TCAs]
  - duloxetine [serotonin and norepinephrine reuptake inhibitors (SNRIs)]
  - mirtazapine [own class]
  - trazodone [own class]
- psychological interventions
  - cCBT without or with minimal support [self-help]
  - cCBT with support [self-help with support]
  - individual BA [individual BT]
  - individual CBT (equal to or over 15 sessions) [individual CT/CBT]
  - group CBT (under 15 sessions) [group CT/CBT]
  - individual problem solving [individual problem solving]
  - non-directive/supportive/person-centred counselling [individual counselling]
  - individual IPT [individual IPT];
  - individual short-term PDPT [individual short-term PDPT]
- physical interventions
  - supervised high intensity individual exercise [individual exercise]
  - supervised high intensity group exercise [group exercise]
  - traditional acupuncture [acupuncture]
- combined interventions
  - CBT individual (equal to or over 15 sessions) + escitalopram [combined individual CT/CBT and antidepressant]
  - Traditional acupuncture + escitalopram [combined acupuncture and antidepressant]
- GP care, reflected in the RCT arms of the reference treatment for more severe depression [placebo]

Model structure

A hybrid decision-analytic model consisting of a decision-tree followed by a three-state Markov model was constructed using Microsoft Office Excel 2013. The model estimated the total costs and benefits associated with provision of effective treatment options in two cohorts of adults with a new episode of less severe depression and more severe depression, respectively. The structure of the model, which aimed to simulate the course of depression and relevant clinical practice in the UK, was also driven by the availability of clinical data.

According to the model structure, hypothetical cohorts of adults with a new episode of depression were initiated on each of the treatment options assessed, as appropriate, according to their level of symptom severity. People in each cohort either completed treatment or discontinued early due to intolerable side effects or other reasons. The duration of a full course of initial treatment was 12 weeks for drugs and GP care; the duration of psychological and physical interventions varied by intervention (ranging between 6 and 16 weeks). The duration of combined interventions was determined by the component with the longest duration. For practical purposes of estimation of QALYs it was assumed that all interventions lasted 12 weeks, without this assumption affecting resource use associated with each intervention. People who discontinued an active treatment early were assumed to switch to a mixture of available treatments for depression or no treatment; people who

discontinued GP care were assumed to move to no treatment. The mixture of available treatments following discontinuation was assumed to have the effectiveness of the baseline reference treatment (GP care) and the mean management cost of people in a depressive episode. Effects of no treatment were obtained from the guideline NMA; the cost of no treatment was zero. The proportion of people moving to no treatment after active treatment discontinuation equalled the probability of discontinuation of GP care.

Following completion of initial treatment or early discontinuation and switch to a mixture of treatments or no treatment, adults with less severe depression (reflecting subthreshold/mild depression) either responded to treatment or failed to meet criteria for response. Response (defined as 50% improvement in depressive symptom score) in adults with less severe depression was assumed to equal remission (defined as a score below the cut-off point for depression on a scale); this was consistent with available data from RCTs on adults with less severe depression that reported both response and remission. Adults with more severe depression (representing moderate and severe depression) either remitted, or responded to treatment without reaching remission, or failed to meet criteria for response. These states (response equalling remission and no/inadequate response for adults with less severe depression; response reaching remission, response not reaching remission and no/inadequate response for adults with more severe depression) were the endpoints of the decision-tree component of the model. From that point on, all people entered the Markov component of the model, which consisted of 3 states: remission (no depressive episode); depressive episode (either due to persistence of the current episode or due to relapse); and death. People who were in remission at the decision-tree endpoint moved to the remission state; those who did not meet criteria for response at the decision-tree endpoint moved to the depressive episode state; and those with more severe depression who responded but did not meet criteria for remission were assumed to either remit (thus moving to the remission state of the Markov model) or remain in a depressive episode (thus moving to the depressive episode state of the Markov model).

The Markov model was run in yearly cycles with a half-cycle correction being applied. In each model cycle, people entering the Markov component of the model could either remain in the same ‘entrance’ state, move between the remission and the depressive episode states, or move to the death state (absorbing state). Adults with more severe depression, who remitted from their 3rd episode following treatment completion, were assumed to receive optimal relapse prevention treatment, as appropriate, depending on the acute treatment that eventually led to remission, as determined by relevant evidence on relapse prevention treatments in the Evidence review C and the resulting guideline recommendations. Details on the specific maintenance treatment received by each cohort are provided at the end of this section. Maintenance antidepressant treatment lasted 2 years; maintenance psychological treatment lasted 1 year. Benefits of all maintenance treatments were assumed to be enjoyed over 2 years, according to available evidence on pharmacological and psychological interventions aiming at relapse prevention and the committee’s expert opinion. Adults with less severe depression who remitted from their 1st episode following treatment completion were assumed to receive no relapse preventive treatment, apart from 3 extra GP visits in the first year and 1 extra GP visit in the second year they spent in the Markov remission state. Those who remitted following completion of antidepressant treatment were assumed to continue antidepressant treatment for another year, i.e. over the first year of the Markov model.

The duration of the Markov model component was 2 years, to enable the full costs and effects of a course of treatment for depression (including acute and, if appropriate, maintenance treatment) to be modelled. Thus, the total time horizon of the economic analysis was 12 weeks of acute treatment (decision-tree) plus 2 years of follow up which included maintenance treatment, as appropriate, for people who remitted following successful acute treatment (Markov model).

The baseline risk of relapse in the Markov remission state depended on the time (one or two years) people spent in this state (the longer people stayed in remission, the lower their risk of relapse) and their number of previous episodes (the higher the number of their previous episodes, the higher their risk of relapse). Therefore, over the 2 years of the Markov component of the model, the risk of relapse experienced by each cohort was determined by their baseline risk of relapse and the efficacy of the (potential) maintenance treatment option received by each cohort. If people relapsed during this period of 2 years, maintenance treatment was discontinued and the preventative benefit of maintenance treatment ceased at the point of relapse.

The probability of remission for each cohort in the depressive episode state depended on the time (one or two years) people spent in this state (the longer people stayed in the depressive episode, the lower their probability of remission) and the severity of depression (less or more severe depression).

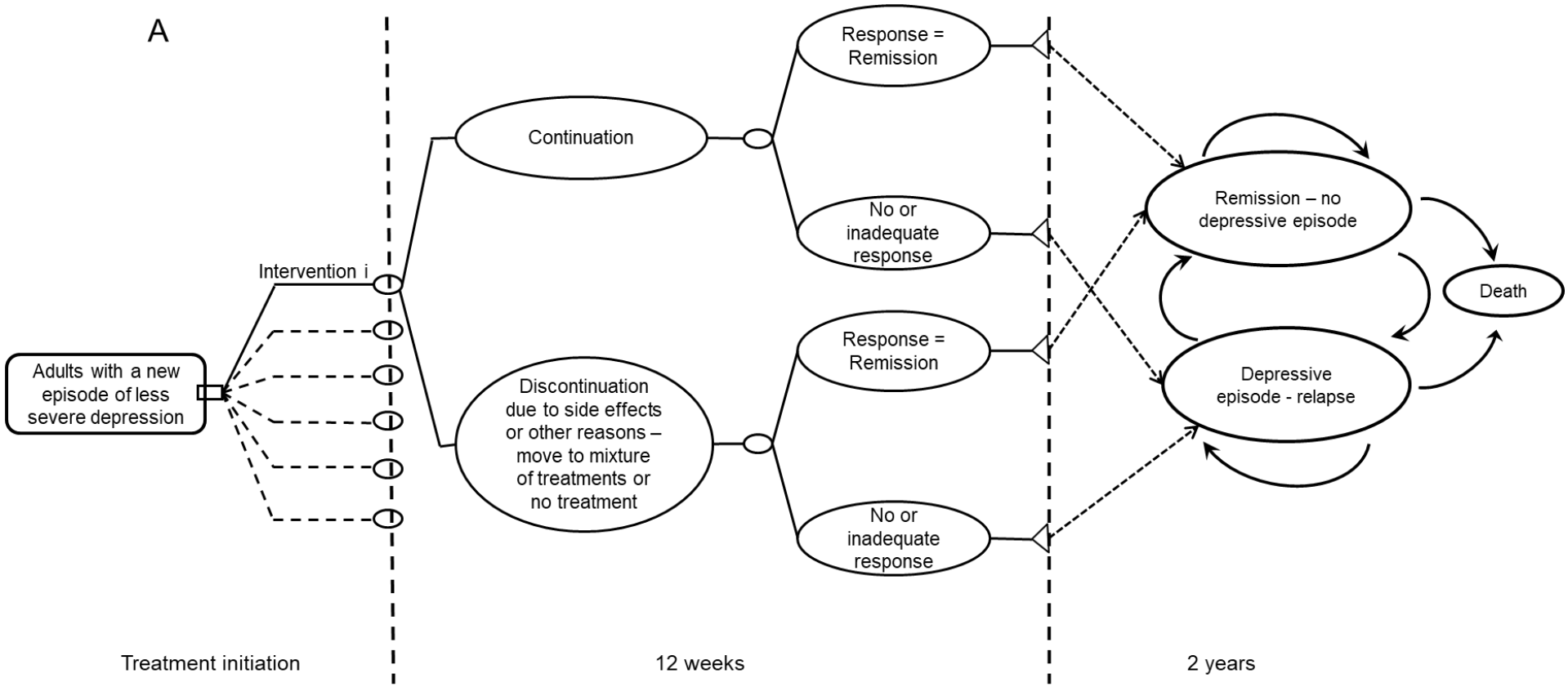
Within the remission and depressive episode states, people entered tunnel states, so that the time they remained in every state (one or two years) could be estimated and a time-dependent probability of relapse or remission, respectively, could be applied.

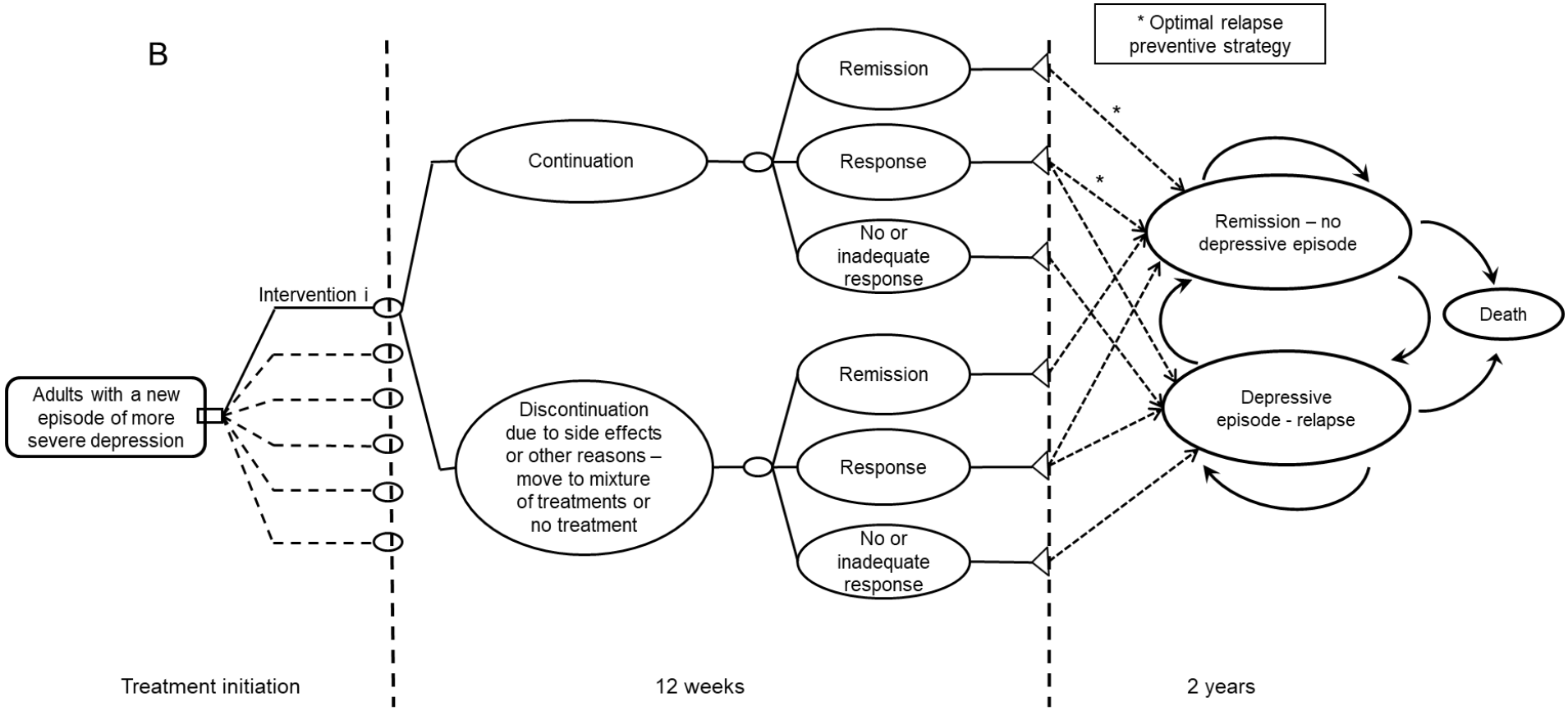
Death was not considered in the acute part of the model. Although the mortality risk in people with depression is higher than that of people in the general population (Cuijpers 2014), suicide (which is the main cause of death in adults with a new episode of depression) is a rare outcome in trials, and there are no substantial differential data on suicide between treatments. The committee expressed the view that consideration of suicide in the acute part of the model would have no significant impact on the relative cost effectiveness between different treatments, and therefore death was considered only in the Markov component of the economic model, for which more relevant, long-term data were available.

Side effects from medication were considered in the model in 2 ways: people who discontinued pharmacological treatment due to side effects were assumed to experience a reduction in their HRQoL over 5 weeks (approximately over the period they were receiving antidepressant treatment) and to incur one extra GP visit. A proportion of people who completed antidepressant treatment was assumed to experience common antidepressant side effects (such as headaches, nausea, agitation, sedation, sexual dysfunction) resulting in a reduction in their HRQoL over the period they experienced side effects, which varied by antidepressant. Moreover, people who experienced side effects from antidepressant treatment were assumed to incur extra costs for the management of their side effects, which comprised GP visits and pharmacological treatment.

The structure of the economic model for interventions for adults with a new episode of depression is shown in Figure 63.

Figure 63. Schematic diagram of the structure of the economic model of treatments for adults with a new episode of (A) less severe depression and (B) more severe depression




B
* Optimal relapse preventive strategy
Adults with a new episode of more severe depression
Intervention i
Continuation
Discontinuation due to side effects or other reasons – move to mixture of treatments or no treatment
Remission
Response
No or inadequate response
Remission
Response
No or inadequate response
*
*
Remission – no depressive episode
Depressive episode - relapse
Death
Treatment initiation
12 weeks
2 years

Relapse-preventive interventions received by adults with more severe depression that responded to (acute) treatment

Adults with more severe depression in their 3rd episode whose depression responded to acute treatment continued treatment aiming at preventing relapses. The choice of continuation treatment was determined by relevant evidence on relapse prevention treatments in the Evidence review C and the resulting guideline recommendations. Table 73 shows the type of continuation treatment people received according to the acute treatment their depression responded to.

Table 73. Continuation treatment aiming at preventing relapses received by people with more severe depression whose depression responded to acute treatment, by type of acute treatment they responded to

Acute treatment	Subsequent maintenance treatment aiming at relapse prevention
More severe depression (remission of 3rd depressive episode)	
Escitalopram	80%: 2 years of maintenance escitalopram treatment 20%: maintenance MBCT + drug tapering
Lofepramine	80%: 2 years of maintenance lofepramine treatment 20%: maintenance MBCT + drug tapering
Duloxetine	80%: 2 years of maintenance duloxetine treatment 20%: maintenance MBCT + drug tapering
Mirtazapine	80%: 2 years of maintenance mirtazapine treatment 20%: maintenance MBCT + drug tapering
Trazodone	80%: 2 years of maintenance trazodone treatment 20%: maintenance MBCT + drug tapering
Individual behavioural activation	80%: 4 sessions of individual behavioural activation 20%: maintenance MBCT
Individual CBT (≥ 15 sessions)	80%: 4 sessions of individual CBT 20%: maintenance MBCT
Individual non-directive counselling	50%: 4 sessions of individual non-directive counselling 50%: maintenance MBCT
Individual IPT	50%: 4 sessions of individual IPT 50%: maintenance MBCT
Individual PDPT	50%: 4 sessions of individual PDPT 50%: maintenance MBCT
Group CBT (under 15 sessions)	80%: maintenance group CBT 20%: maintenance MBCT
cCBT without or with minimal support	50%: maintenance group CBT 50%: maintenance MBCT
cCBT with support	50%: maintenance group CBT 50%: maintenance MBCT
Individual problem solving	50%: maintenance group CBT 50%: maintenance MBCT
Individual exercise	50%: maintenance group CBT 50%: maintenance MBCT
Group exercise	50%: maintenance group CBT 50%: maintenance MBCT
Acupuncture	50%: maintenance group CBT 50%: maintenance MBCT

Acute treatment	Subsequent maintenance treatment aiming at relapse prevention
CBT individual (over 15 sessions) + escitalopram	80%: 2 years of maintenance escitalopram treatment 20%: 4 sessions of individual CBT + drug tapering
Acupuncture + escitalopram	80%: 2 years of maintenance escitalopram treatment 20%: maintenance MBCT + drug tapering
GP care	100%: GP care follow-up

Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services, as recommended by NICE (NICE 2014). Costs consisted of intervention costs (drug acquisition, staff time for provision of pharmacological, psychological, physical and combined therapies), including optimal maintenance treatments for relapse prevention in people who remitted, as appropriate, as well as costs associated with the further management of people who discontinued the initiated treatment, those who did not remit or people who relapsed following remission, which included drug acquisition, primary care, hospitalisation, outpatient visits, psychological therapies, and also accident and emergency visits. Costs of management of common side effects from antidepressants in people receiving pharmacological treatment and healthcare costs incurred by people in remission (potentially unrelated to the treatment of depression) were also considered in the analysis. The cost year was 2020.

The measure of outcome was the Quality Adjusted Life Year (QALY), which incorporated utilities associated with the health states of remission, response without reaching remission, no or inadequate response, as well as utility decrements due to intolerable side effects and common (tolerable) side effects associated with antidepressant and combined treatment (both acute and maintenance).

Relative effects on efficacy, acceptability and tolerability of treatments for a new depressive episode and methods of evidence synthesis

Data on the relative risks of acceptability and efficacy for interventions considered in the economic modelling for a new episode of depression in adults with less severe depression and adults with more severe depression were derived from the NMAs of interventions for adults with a new depressive episode that were undertaken for this guideline. Details on the methods and results of the NMAs, which were conducted in OpenBUGS 3.2.3 (www.openbugs.net) are provided in appendix M. The principles of OpenBUGS are the same as of WinBUGS (Lunn 2000; Spiegelhalter 2003). In summary, binomial likelihood and logit models were used (Dias 2011 [last updated 2016]), to allow estimation of odds ratios of each treatment versus baseline for each outcome of interest, which were then applied onto the respective baseline risk of each outcome. For the economic analysis the first 100,000 iterations undertaken in OpenBUGS were discarded and another 300,000 were run, thinned by 30, so as to obtain 10,000 iterations that populated the economic model.

Although, as discussed in the Evidence review C, appendix J, the probability of recovery in people with depression is reduced over time following a Weibull distribution, the logit model was considered appropriate to use for the estimation of relative effects between acute treatments expressed as odds ratios over a relatively short period of time.

For each population, the following parameters were obtained from the NMAs, expressed as odds ratios versus a selected baseline:

- discontinuation (for any reason)
- discontinuation due to side effects, in those discontinuing pharmacological treatment
- response in those completing treatment
- remission in those completing treatment (only for adults with more severe depression)

These outcomes were a priori selected to inform the economic model as, according to the committee's advice, they reflected main outcomes and events associated with treatment of adults with depression in routine practice.

These data were combined with respective baseline risks for each outcome in adults with less severe depression and in adults with more severe depression, in order to estimate the probabilities of events of each intervention in each endpoint of the decision-tree component of the model, for each population of interest.

For adults with less severe depression, the discontinuation due to side effects outcome was informed by an indirect comparison between SSRIs and TCAs, using placebo as the common comparator.

A NMA of remission in those completing treatment for adults with less severe depression was also conducted; however, available data were very limited and covered only a minority of the treatment classes included in economic modelling. Available data from studies reporting both response and remission data in this population suggested that the probability of response to treatment (defined as at least 50% reduction in baseline depressive symptom score) was approximately equal to the probability of remission (defined as a score below a cut-off point on a scale). This is not unexpected, considering that this population includes adults with mild or subthreshold depression, with a low baseline depressive symptom score, and therefore response to treatment most often meets criteria for remission as well. For this reason, and due to lack of remission data for the majority of the interventions considered for this population, the economic model assumed that adults with less severe depression who respond to treatment are also remitters.

It needs to be noted that, originally, the outcome of interest in order to populate the economic model with numbers of people remitting was remission conditional on response (that is, probability of remission in those responding to treatment). However, the networks constructed for this outcome were sparse and/or disconnected and covered a limited number of interventions, and therefore were not informative for the economic model. For this reason, remission in those completing treatment was selected as an outcome instead, to allow, in combination with data on response in those completing treatment, calculation of numbers of people who responded and remitted. When running the probabilistic analysis, the number of people reaching remission was not allowed to exceed the number of people responding to treatment. In iterations where the probability of remission exceeded the probability of response, the number of people in remission was forced to equal that of people in response (so that all people who responded also remitted in those iterations).

Relative effects were obtained from the NMAs for the individual interventions modelled, with the exception of discontinuation due to side effects in those discontinuing treatment, where drug class effects were used to increase the evidence base. However, when intervention-specific data on an outcome were not available for an intervention included in economic modelling, then either class effects (for single interventions) or effects from another similar intervention within the class (for combined interventions) were used instead.

As described later under 'Baseline probabilities', for two of the outcomes (response in those completing treatment and remission in those completing treatment) the chosen baseline was GP care, reflected in the NMA reference treatment (TAU for less severe depression and placebo for more severe depression). For the other two outcomes (discontinuation and discontinuation due to side effects in those discontinuing treatment) the selected baseline treatment was SSRIs.

For a number of guideline NMA outcomes, bias-adjusted models were run to explore potential bias associated with small study size. These outcomes were the SMD, selected as the primary clinical outcome, and the outcomes of discontinuation and response in completers, selected as the main NMA outcomes that informed the economic analysis with the highest anticipated impact on the economic results (see appendix M). The NMA models

on discontinuation and response in completers for adults with less severe depression did not suggest evidence of small study bias. However, the respective models for adults with more severe depression suggested evidence of bias on both outcomes in the comparisons of active versus inactive treatments or active treatments versus non-directive counselling in studies with larger variance (that is, in smaller studies); hence, a probabilistic bias-adjusted economic analysis was conducted in this population, using bias-adjusted data on these two outcomes.

The results of the base-case NMAs that were used to populate the economic model are provided in Table 74 for adults with less severe depression and Table 75 for adults with more severe depression. The results of the bias-adjusted NMAs of discontinuation and response in completers that informed the bias-adjusted model of treatments for adults with more severe depression are shown in Table 76. Full results for all classes and interventions, including those not considered in the economic analysis, as well as model fit statistics, heterogeneity and results of inconsistency checks for each outcome are provided in appendix M and supplements B5 and B6.

In summary, for less severe depression, and relative to the size of the intervention effect estimates, the between trial heterogeneity was found to be moderate for both discontinuation due to any reason, and for response in completers. Some evidence of inconsistency was identified for the response in completers outcome.

For more severe depression, and relative to the size of the intervention effect estimates, the between trial heterogeneity was found to be moderate for discontinuation due to any reason, discontinuation due to side effects from medication in those discontinuing treatment, and response in completers, and small for remission in completers. Some evidence of inconsistency was identified for discontinuation, discontinuation due to side effects from medication in those discontinuing treatment, and remission in completers.

It is noted that relative effects and rankings of treatments in the response in completers outcome may differ from those observed for the standardised mean difference (SMD) and response in those randomised outcomes that were considered in the clinical analysis. Possible explanations for this discrepancy include:

- Different studies have been included in different analyses (depending on availability of reported outcome data in each study)
- There was a different way for accounting of drop-outs in each study outcome and each analysis: the response in completers outcome considered improvement after excluding those who have discontinued treatment. On the other hand, the SMD analysis prioritised use of continuous scale data for all trial participants where available, if a study used data imputation methods for trial drop-outs; otherwise completer data were used. Trials that imputed data reported different methods for data imputation, such as last observation carried forward (LOCF), multiple imputation, or baseline observation carried forward (BOCF). The NMA of response in those randomised included a mixture of dichotomous response data (where people who discontinued were considered as non-responders) as a priority, in studies where such dichotomous data were available, and continuous data, where RCTs did not report dichotomous response data. The amount of continuous data and the method of imputation included in the response in those randomised analyses have unavoidably affected the results of these analyses.

The networks of all NMAs that informed the economic analysis are provided in appendix M.

Table 74. Results of the NMAs that informed the economic analysis of interventions for a new depressive episode in adults with less severe depression: log-odds ratios versus baseline for each outcome of interest

Intervention [Class]	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)		
	Discontinuation versus sertraline	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [TAU]
Sertraline [SSRIs]	Baseline	Baseline	2.01 (0.03 to 3.98)
	N=326	Nclass=31	N=50
Loferpamine [TCAs]	0.21 (-1.32 to 1.78)	3.32 (-0.22 to 6.88)	3.15 (0.04 to 6.23)
	N=32	Nclass=40	N=23
Computerised CBT without or with minimal support [Self-help]	-0.64 (-5.55 to 2.92)	Not relevant	0.85 (-0.47 to 2.15)
	N=3,173		N=607
Computerised CBT with support [Self-help with support]	-0.65 (-5.61 to 2.94)	Not relevant	0.95 (-1.03 to 2.86) [class effect]
	N=428		Nclass=327
Individual BA [BT individual]	-1.80 (-7.09 to 2.55)	Not relevant	1.83 (-0.29 to 3.93)
	N=153		N=111
Group BA [BT group]	-0.33 (-5.26 to 3.33)	Not relevant	3.02 (1.05 to 5.02)
	N=107		N=47
Individual CBT (<15 sessions) [individual CT/CBT]	-1.42 (-6.30 to 2.17)	Not relevant	1.79 (0.15 to 3.43)
	N=402		N=233
Group CBT (<15 sessions) [group CT/CBT]	-0.94 (-5.95 to 2.81)	Not relevant	4.63 (2.44 to 6.87)
	N=283		N=59
Individual problem solving [individual problem solving]	-0.50 (-5.41 to 3.15)	Not relevant	0.26 (-1.14 to 1.66)
	N=159		N=98
Non-directive/supportive/person-centred counselling [Counselling]	-1.80 (-6.86 to 2.01)	Not relevant	1.16 (-2.55 to 4.79)
	N=125		N=39

Intervention [Class]	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)		
	Discontinuation versus sertraline	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [TAU]
Individual IPT [individual IPT]	-0.56 (-5.63 to 2.79)	Not relevant	1.04 (-0.28 to 2.36)
	N=108		N=125
Individual short-term PDPT [individual short term PDPT]	-2.12 (-7.17 to 1.75)	Not relevant	1.63 (-1.18 to 4.45)
	N=53		N=43
Group MBCT [mindfulness or meditation group]	-0.83 (-5.76 to 2.82)	Not relevant	1.72 (0.00 to 3.40)
	N=167		N=73
Supervised high intensity individual exercise [individual exercise]	-1.43 (-6.54 to 2.35)	Not relevant	1.16 (-0.47 to 2.79)
	N=39		N=43
Supervised high intensity group exercise [group exercise]	-0.86 (-5.89 to 2.87)	Not relevant	1.43 (-0.12 to 2.95)
	N=121		N=136
GP care [TAU]	-0.81 (-5.77 to 2.70)	Not relevant	Baseline
	N=1,005		N=395
No treatment [No treatment]	Not relevant	Not relevant	-0.16 (-1.43 to 1.10)
			N=1,033

BA: behavioural activation; BT: behavioural therapy; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant

Table 75. Results of the base-case NMAs that informed the economic analysis of interventions for a new depressive episode in adults with more severe depression: log-odds ratios versus baseline for each outcome of interest

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)			
	Discontinuation versus escitalopram	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [placebo]	Remission in treatment completers versus GP care [placebo]
Escitalopram [SSRIs]	Baseline	Baseline	0.81 (0.60 to 1.00)	0.56 (0.44 to 0.71)
	N=5,627	Nclass=661	N=3,396	N=2,457
Lofepramine [TCAs]	0.10 (-0.18 to 0.33)	0.69 (0.18 to 1.21)	1.14 (0.81 to 1.46)	0.70 (-0.12 to 1.24)
	N=296	Nclass=963	N=188	N=55
Duloxetine [SNRIs]	0.14 (-0.02 to 0.33)	0.40 (-0.07 to 0.86)	0.99 (0.75 to 1.23)	0.75 (0.62 to 0.88)
	N=5,226	Nclass=1,272	N=3,700	N=3,674
Mirtazapine	0.06 (-0.14 to 0.26)	0.03 (-0.37 to 0.43)	1.02 (0.70 to 1.33)	0.61 (0.34 to 0.89)
	N=2,637	N=692	N=1,845	N=645
Trazodone	0.35 (0.10 to 0.60)	0.26 (-0.24 to 0.77)	0.68 (0.28 to 1.09)	0.53 (0.26 to 0.81)
	N=1,430	N=365	N=1,003	N=552
cCBT without or with minimal support [Self-help]	-0.22 (-1.08 to 0.67)	Not relevant	0.12 (-1.79 to 1.89)	1.38 (-0.55 to 3.61) [class effect]
	N=115		N=20	Nclass=147
cCBT with support [Self-help with support]	-0.19 (-0.90 to 0.51)	Not relevant	0.82 (-0.36 to 2.02)	0.95 (0.14 to 1.75)
	N=290		N=114	N=165
Individual BA [Individual BT]	-0.65 (-1.33 to 0.03)	Not relevant	1.42 (0.09 to 2.77)	1.08 (0.45 to 1.71)
	N=595		N=310	N=320
Individual CBT (≥15 sessions) [individual CT/CBT]	-0.43 (-0.88 to 0.01)	Not relevant	1.22 (0.55 to 1.89)	1.09 (0.61 to 1.56)
	N=461		N=348	N=391
Group CBT (<15 sessions) [group CT/CBT]	-0.31 (-1.32 to 0.68)	Not relevant	0.99 (-0.27 to 2.21)	0.29 (-0.84 to 1.37)
	N=162		N=64	N=32

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)			
	Discontinuation versus escitalopram	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [placebo]	Remission in treatment completers versus GP care [placebo]
Individual problem solving [individual problem solving]	-0.64 (-1.47 to 0.16)	Not relevant	2.16 (0.78 to 3.55)	1.15 (0.19 to 2.14)
	N=448		N=123	N=191
Non-directive/supportive/person-centred counselling [Counselling]	-0.35 (-1.15 to 0.45)	Not relevant	1.50 (0.08 to 2.92)	0.30 (-0.85 to 1.47)
	N=332		N=216	N=103
Individual IPT [individual IPT]	-0.68 (-1.51 to 0.15)	Not relevant	0.72 (-0.31 to 1.73)	1.00 (0.34 to 1.67)
	N=63		N=132	N=89
Individual short-term PDPT [individual short term PDPT]	0.04 (-0.85 to 0.95)	Not relevant	1.58 (-0.94 to 4.06)	0.50 (-0.47 to 1.45)
	N=56		N=16	N=42
Supervised high intensity individual exercise [individual exercise]	0.14 (-0.88 to 1.23)	Not relevant	2.40 (-0.31 to 5.05)	0.32 (-0.47 to 1.20)
	N=162		N=47	N=109
Supervised high intensity group exercise [group exercise]	0.26 (-0.42 to 0.93)	Not relevant	2.02 (0.17 to 4.08)	0.63 (0.02 to 1.27)
	N=124		N=18	N=80
Traditional acupuncture [Acupuncture]	-0.25 (-1.28 to 0.64)	Not relevant	-0.17 (-1.38 to 1.01)	0.10 (-1.58 to 1.80)
	N=102		N=130	N=42
Individual CBT (≥15 sessions) + escitalopram [Combined individual CT/CBT individual + AD]	-0.32 (-1.22 to 0.51) [borrowed from individual CBT (≥15 sessions) + imipramine]	1 [risk same as escitalopram]	1.84 (0.61 to 3.00) [borrowed from individual CBT (≥15 sessions) + any SSRI]	1.72 (0.81 to 2.91) [borrowed from individual CBT (≥15 sessions) + imipramine]
	N=25		N=43	N=16
Traditional acupuncture + escitalopram [combined acupuncture + AD]	-0.27 (-1.51 to 0.96) [borrowed from traditional	1	4.07 (2.97 to 5.17) [borrowed from traditional	0.46 (-0.54 to 1.47) [borrowed from traditional

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)			
	Discontinuation versus escitalopram	Discontinuation due to side effects in those discontinuing versus SSRIs [class effects reported]	Response in treatment completers versus GP care [placebo]	Remission in treatment completers versus GP care [placebo]
	acupuncture + paroxetine]	[risk same as escitalopram]	acupuncture + any SSRI]	acupuncture + paroxetine]
	N=54		N=185	N=51
GP care [placebo]	0.13 (0.02 to 0.24)	Not relevant	Baseline	Baseline
	N=16,577		N=9,333	N=5,850
No treatment	Not relevant	Not relevant	-0.27 (-1.40 to 0.86)	0.17 (-0.52 to 0.87)
			N=266	N=299

AD: antidepressant; BA: behavioural activation; BT: behavioural therapy; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant

Table 76. Results of the bias-adjusted NMAs that informed the economic analysis of interventions for a new depressive episode in adults with more severe depression: log-odds ratios versus baseline for each outcome of interest [of those where evidence of bias was tested and identified]

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)	
	Discontinuation versus escitalopram	Response in treatment completers versus GP care [placebo]
Escitalopram [SSRIs]	Baseline	0.65 (0.43 to 0.85)
	N=5,627	N=3,396
Lofepramine [TCAs]	0.11 (-0.16 to 0.34)	0.87 (0.53 to 1.20)
	N=296	N=188
Duloxetine [SNRIs]	0.14 (-0.01 to 0.33)	0.84 (0.59 to 1.08)
	N=5,226	N=3,700
Mirtazapine	0.07 (-0.13 to 0.26)	0.77 (0.44 to 1.10)
	N=2,637	N=1,845

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)	
	Discontinuation versus escitalopram	Response in treatment completers versus GP care [placebo]
Trazodone	0.34 (0.08 to 0.59)	0.50 (0.10 to 0.91)
	N=1,430	N=1,003
cCBT without or with minimal support [Self-help]	-0.19 (-1.10 to 0.73)	-0.20 (-2.26 to 1.67)
	N=115	N=20
cCBT with support [Self-help with support]	-0.16 (-0.91 to 0.58)	0.39 (-0.87 to 1.68)
	N=290	N=114
Individual BA [Individual BT]	-0.68 (-1.39 to 0.02)	1.18 (-0.19 to 2.49)
	N=595	N=310
Individual CBT (≥15 sessions) [individual CT/CBT]	-0.36 (-0.82 to 0.10)	0.92 (0.21 to 1.62)
	N=461	N=348
Group CBT (<15 sessions) [group CT/CBT]	-0.21 (-1.30 to 0.88)	0.51 (-0.76 to 1.81)
	N=162	N=64
Individual problem solving [individual problem solving]	-0.71 (-1.62 to 0.18)	2.03 (0.61 to 3.46)
	N=448	N=123
Non-directive/supportive/person-centred counselling [Counselling]	-0.33 (-1.15 to 0.51)	1.38 (-0.06 to 2.83)
	N=332	N=216
Individual IPT [individual IPT]	-0.64 (-1.49 to 0.18)	0.43 (-0.65 to 1.50)
	N=63	N=132
Individual short-term PDPT [individual short term PDPT]	0.11 (-0.84 to 1.08)	1.31 (-1.21 to 3.81)
	N=56	N=16
Supervised high intensity individual exercise [individual exercise]	0.21 (-0.82 to 1.30)	1.47 (-1.69 to 4.73)
	N=162	N=47
	0.30 (-0.41 to 1.01)	1.63 (-0.34 to 3.78)

Intervention	Mean log-odds ratios of every intervention versus baseline (95% credible intervals)	
	Discontinuation versus escitalopram	Response in treatment completers versus GP care [placebo]
Supervised high intensity group exercise [group exercise]	N=124	N=18
Traditional acupuncture [Acupuncture]	-0.37 (-1.36 to 0.57)	-0.26 (-1.49 to 0.93)
	N=102	N=130
Individual CBT (≥15 sessions) + escitalopram [Combined individual CT/CBT individual + AD]	-0.28 (-1.19 to 0.59) [borrowed from individual CBT (≥15 sessions) + imipramine]	1.68 (0.43 to 2.82) [borrowed from individual CBT (≥15 sessions) + any SSRI]
	N=25	N=43
Traditional acupuncture + escitalopram [combined acupuncture + AD]	-0.14 (-1.39 to 1.10) [borrowed from traditional acupuncture + paroxetine]	3.85 (2.74 to 4.95) [borrowed from traditional acupuncture + any SSRI]
	N=54	N=185
GP care [placebo]	0.08 (-0.03 to 0.21)	Baseline
	N=16,577	N=9,333
No treatment	Not relevant	-0.24 (-1.40 to 0.94)
		N=266

AD: antidepressant; BA: behavioural activation; BT: behavioural therapy; CBT: cognitive behavioural therapy; CT: cognitive therapy; IPT: interpersonal psychotherapy; PDPT: psychodynamic psychotherapy; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant

Baseline probabilities

The baseline probabilities of the 4 outcomes of interest were estimated based on published literature and the committee's expert opinion and were applied in the decision-tree component of the economic model. All relative effects of the other interventions versus the intervention serving as baseline were applied onto the baseline probability in order to obtain the absolute probability of every intervention assessed in the economic analysis for each outcome of interest.

The committee expressed the view that absolute probabilities reported in RCTs included in the NMAs did not reflect probabilities seen under non-interventional conditions and routine clinical practice, and therefore these were not utilised in the economic analysis.

Baseline probability of early discontinuation (for any reason)

Burton 2012 analysed prescription data from a Scottish primary care database of adults who commenced treatment with an eligible antidepressant between April 2007 and March 2008 across 237 Scottish practices. Eligible antidepressants comprised SSRIs, SNRIs, lofepramine and trazodone. The authors identified 28,027 people who initiated treatment with an eligible antidepressant over this period, of whom 24.6% did not continue treatment beyond 30 days (they discontinued treatment within the first 30 days) and 44.5% did not continue treatment beyond 90 days (they discontinued treatment within the first 90 days). The authors did not report discontinuation rates by level of severity of depression or by specific drug or drug class.

Hansen 2004 reported rates of discontinuation (defined as people not purchasing antidepressants in the 6 months following first prescription) following analysis of data on 4,860 adult first-time users of antidepressants (regardless of diagnosis) who presented in 174 general practices in Denmark between January 1998 and June 1999. The discontinuation rate was 30.5% for adults prescribed new generation antidepressants, mainly SSRIs (n=4,275) and 56.4% for adults prescribed TCAs (n=585). No information was provided on discontinuation rates in relation to the level of symptom severity.

Bull 2002 assessed the rates of discontinuation at 3 and 6 months in 672 adults that were started on an SSRI (fluoxetine or paroxetine) by a psychiatrist or primary care physician for a new or recurrent case of depression between January and September 1998 in the USA. Participants were conducted via a telephone survey. At 3 months, 34% had discontinued their initiated SSRI.

Goethe 2007 reported discontinuation data on 406 adults with severe depression who were treated with SSRIs in a secondary care setting (208 as outpatients and 198 as inpatients) in the USA between July 2001 and January 2003. The reported discontinuation rate at 3 months was 24.6%.

Lewis 2004 reported rates of early discontinuation among 26,888 adults who filled an SSRI prescription, by analysing data from a large database in the USA. Of these, 61.3% were seen in primary care, 14.9% were treated by psychiatrists and another 23.8% were treated by another medical specialist. Early discontinuation was defined as failure to refill a prescription for any antidepressant medication within 30 days of the end of the first SSRI prescription. The authors reported early discontinuation of 37.1% for adults prescribed an SSRI by primary care providers, 31.8% for those treated by psychiatrists and 41.4% for those treated by other medical specialists. No information was provided on discontinuation rates in relation to level of severity of symptoms.

Olfson 2006 analysed data on 829 adults with depression who were initiated on antidepressant treatment, derived from the household component of the Medical Expenditure Panel Survey conducted in the USA for the years 1996 to 2001. The authors reported rates

of discontinuation during the first 30 days of treatment and between 31-90 days of treatment by mental status. In the first 30 days of treatment, discontinuation reached 42.7% in adults with “excellent to good” mental status and 42.0% in adults with “fair or poor” mental status. Between 31-90 days of treatment, discontinuation reached 57.3% in adults with “excellent to good” mental status and 41.1% in adults with “fair or poor” mental status. In total, discontinuation over 90 days reached 75% and 65% in adults with “excellent to good” and those with “fair or poor” mental status, respectively. Discontinuation was lower in people taking SSRIs or SNRIs (40.9% in first 30 days, 48.0% in 31-90 days) compared with other new medications (49.9% in first 30 days, 63.0% in 31-90 days) and TCAs and other old antidepressants (45.2% in first 30 days, 68.2% in 31-90 days). Discontinuation in the first 30 days was lower in adults who had private health insurance (39.9%) compared with those who had public (48.6%) or no (50.6%) insurance. No other information was provided on discontinuation rates in relation to severity of depressive symptoms or type of provider (primary or specialist care).

The committee reviewed the data reported in the studies. The figures of 24.6% and 44.5% for continuation up to 30 and 90 days, respectively, that were reported by Burton 2012 are directly relevant to primary care practice in the UK; the figure of 44.5% is likely to include people who took a full first course of treatment but did not continue because of treatment failure (lack of efficacy); therefore the risk of discontinuation of initiated treatment prior to completion of a full course lies between the two figures of 24.6% and 44.5%. It is likely that the figure is relevant to SSRIs, since these are among the most commonly used antidepressants. Hansen 2004 reported a discontinuation risk of 30.5% over a period of 6 months for SSRIs prescribed in primary care in Denmark. The USA figures are higher, as Lewis 2004 reported a 37.1% discontinuation within 30 days for SSRIs prescribed in primary care, while Olfson 2006 reported the highest rates, 75% and 65% over 90 days, in adults with ‘excellent to good’ and those with ‘fair or poor’ mental status, respectively. Discontinuation rates were reported to be higher in people treated in primary compared with specialist care.

Following consideration of the data and the committee’s expert opinion, estimated figures of 37% for early discontinuation of SSRIs in adults with less severe depression, and 34% for early discontinuation of SSRIs in adults with more severe depression were used. These figures are within the range of percentages reported by Burton 2012 for 30 and 90 days, but lower than the figures reported by Olfson 2006 over 90 days. Discontinuation was assumed to be higher in adults with less severe depression, based on data reported in Olfson 2006 and the committee’s expert opinion.

Using the guideline NMA relative SSRI class and individual drug effects versus placebo, the figure of 0.38 was estimated and used as the baseline probability of discontinuation for sertraline, in the economic analysis for adults with less severe depression. The figure of 0.34 was estimated and used as the baseline probability of discontinuation for escitalopram in the economic analysis for adults with more severe depression.

Baseline probability of discontinuation due to side effects in those discontinuing treatment early

Discontinuation due to side effects was relevant to cohorts treated with pharmacological treatments or combined treatments with a pharmacological intervention component.

Bull 2002 reported reasons for drug discontinuation at 3 and 6 months in 672 adults that were started on an SSRI (fluoxetine or paroxetine) by a psychiatrist or primary care physician for a new or recurrent case of depression between January and September 1998 in the USA. Participants were conducted via a telephone survey. Overall, 15% of people who were initiated on a SSRI discontinued due to intolerable side effects over the first 3 months of the study.

Goethe 2007 reported discontinuation data on 406 adults with severe depression who were treated with SSRIs in a secondary care setting (208 as outpatients and 198 as inpatients) in the USA between July 2001 and January 2003. Overall, 13% of people who were initiated on an SSRI discontinued due to intolerable side effects over the first 3 months of the study.

The risk of discontinuation due to side effects was considered to be independent of the depressive symptom severity. A risk of 0.15 was therefore applied to people initiated on SSRIs with both less severe and more severe depression. Since the risk of discontinuation with SSRI treatment was estimated to be 0.38 (sertraline) in adults with less severe depression and 0.34 (escitalopram) in adults with more severe depression, the estimated risk of discontinuation due to side effects in those discontinuing these specific SSRI treatments was estimated to be 0.15/0.38 = 0.39 (sertraline) and 0.15/0.34 = 0.44 (escitalopram) in adults with less severe depression and more severe depression, respectively.

The figure of 0.39 was used as the baseline probability of discontinuation due to side effects in those discontinuing sertraline in the economic analysis for adults with less severe depression. The figure of 0.44 was used as the baseline probability of discontinuation due to side effects in those discontinuing escitalopram in the economic analysis for adults with more severe depression.

Baseline probability of response and remission in treatment completers

The only study identified in the literature reporting relevant data by level of depressive symptom severity was conducted by Simon 1999, who reported 12-month outcomes of 948 people with major depression attending primary care services who participated in a multinational, longitudinal study conducted at 15 sites in 14 countries including the UK. All study participants had been assessed at baseline by study researchers using the Composite International Diagnostic Interview (CIDI), the 28-item General Health Questionnaire (GHQ), and the Brief Disability Questionnaire (BDQ) and were classified as having mild, moderate or severe major depression. Participants also underwent assessment by their primary care physicians at baseline; depression or a psychological disorder and a comorbid condition was correctly recognised by physicians in 42% of them. However, no information on follow-up care or treatment received was available for any of the participants. At 12 month follow-up the diagnostic status (ICD-10 depressive disorder) of participants was reported by their baseline symptom severity, stratified according to whether they had been recognised by their physicians at baseline. Recognised and unrecognised groups did not differ significantly in change in diagnostic status from baseline. Results were consistent across study sites.

Table 77 shows the 12-month diagnostic status of people who had been diagnosed with mild, moderate and severe depression at baseline, and who had been recognised by their physician to have a depression or another psychological disorder.

Table 77. Diagnostic status at 12 months of people with major depression that were diagnosed by their physicians at baseline, by baseline severity status, as reported in Simon 1999

12-month status	Baseline mild depression	Baseline moderate depression	Baseline severe depression
Recovery	79.3%	64.5%	54.9%
Mild depression	6.9%	3.2%	7.8%
Moderate depression	6.9%	19.4%	9.8%
Severe depression	6.9%	12.9%	27.5%
TOTAL	100.0%	100.0%	100.0%

It can be seen that at 12-months the probability of recovery is highest for people with mild depression (0.79), lower for people with moderate depression (0.65) and lowest for people

with severe depression at baseline (0.55). Based on the data above, it is possible to estimate the probability of improvement from baseline to 12 months for each category of symptom severity, considering improvement as movement to a lower level of severity or recovery. For mild depression the probability of improvement equals that of recovery (0.79); for moderate depression improvement of status is reflected by recovery or a move to mild depression (0.68 in total); and for severe, the probability of improvement is reflected in recovery or reduction of symptoms from severe to mild or moderate (0.73).

These data formed the basis for estimating the 3-month probability of response (as expressed by improvement) and remission at baseline in the economic model for adults with less severe depression and those with more severe depression. Although the study reported data on both people recognised by their physicians as having a psychological disorder and those that were not recognised, the economic analysis utilised data on people whose disorder was recognised by their physicians, as the study population of the economic analysis comprises adults with recognised depression initiating treatment. The committee advised that reported data be used to represent the baseline probability of response and remission in those completing GP care. This was decided as there was no information in the study on the specific treatment received by study participants; the committee considered that a mixture of treatments would have been received, with some people having received more intensive treatment and some others less intensive or no treatment. The committee inspected the available 12-month recovery and improvement data reported for each level of symptom severity and expressed the view that, on balance, they reflect baseline changes in status that are observed under GP care.

As reported in Evidence review C, appendix J, synthesis of remission data from cohort studies following people with depression showed that the probability of remission in people with depression follows a Weibull distribution in which the remission rate is proportional to a power of time. People have a higher probability of remission soon after initiation of the depressive episode, and this probability is reduced over time, as they remain in that episode; the cumulative hazard rate for the Weibull distribution is given by the following mathematical formula:

$$H(t) = \lambda t^{\gamma}$$

where lambda (λ) and gamma (γ) are the scale and shape parameters of the distribution, respectively.

A literature review and synthesis of relevant cohort data determined the parameters of the Weibull distribution characterising the probability of remission over time. These parameters, shown in Table 78, were estimated using data from studies on cohorts with depression followed over long periods of time, irrespective of their level of symptom severity (Gonzales 1985, Holma 2008, Keller 1981, 1984, 1992; Mueller 1996; Skodol 2011). Details of the literature review and data synthesis are provided in Evidence review C, appendix J.

Table 78. Parameters of the Weibull distribution of the probability of remission over time, in people experiencing a depressive episode

Parameter	Mean	SD	Median	95% Credible intervals
Lambda	1.16	0.04	1.16	1.08 to 1.24
Gamma	0.42	0.03	0.42	0.37 to 0.47

In order to estimate the 3-month probabilities of remission and response in people completing GP care it was assumed that both followed a Weibull distribution with the same shape parameter gamma across all symptom severity levels that was equal to that estimated from synthesis of cohort studies (Table 78). The lambda parameter for response and remission at each level of severity was estimated from the available 12-month data (Simon 1999). The estimated 3-month probabilities of response and remission at each symptom

severity level as well as the estimated hazard ratios of response and remission at each level of severity versus the 'baseline' remission, estimated from data synthesis, are shown in Table 79.

Table 79. Parameters of the Weibull distribution and 3-month probabilities of response and remission, in people experiencing a depressive episode according to their level of symptom severity

Mean values	Baseline remission – based on synthesis of studies	Data based on Simon 1999 for people with major depression recognised by their physician					
Parameter		Mild depression		Moderate depression		Severe depression	
		Resp	Remis	Resp	Remis	Resp	Remis
12-month probability	0.69	0.79	0.79	0.68	0.65	0.73	0.55
Hazard (lambda)	1.16	1.58	1.58	1.13	1.04	1.29	0.80
Hazard ratio vs baseline (lambda)	1 (reference)	1.36	1.36	0.97	0.89	1.11	0.69
Gamma	0.42						
3-month probability	0.46	0.57	0.57	0.45	0.43	0.50	0.35
Notes: Resp: response; Remis: remission							

The 3-month probability of response (and remission) for adults with less severe depression was equal to that for people with mild depression (0.57). The 3-month probabilities of response and remission for adults with more severe depression were estimated as an average of respective probabilities estimated for people with moderate and severe depression (0.48 and 0.39, respectively).

When running the probabilistic analysis, the number of people reaching remission were not allowed to exceed the number of people responding to treatment in the population with more severe depression. In iterations where the probability of remission exceeded the probability of response, the number of people in remission was forced to equal that of people in response (so that all people who responded also remitted in those iterations).

Other clinical input parameters

Progression of depression in adults with more severe depression who responded to acute treatment without reaching remission

Adults with more severe depression who responded to initial treatment but did not meet criteria for remission at the end of the 12 weeks of treatment were assumed to receive a course of further treatment and either remit or remain in a depressive episode. For the purposes of simplicity, people in this branch of the model were assumed to move to one of the two respective states of the Markov model (remission or depressive episode) at the end of 12 weeks, although in reality this transition would not occur immediately. The probability of moving to the Markov remission state was based on the committee's expert opinion, due to lack of relevant data. According to this, the probability of adults with more severe depression moving to remission following response to treatment (but without remission) at 12 weeks was 0.30.

Risk of relapse in the Markov component of the economic model

The risk of relapse in people who were in the remission state in the Markov component of the economic model was determined by the time spent in the remission state (one or two years), the number of previous episodes experienced by each cohort assessed in the analysis, and,

in people with more severe depression who received maintenance treatment, by the efficacy of relapse preventive treatment.

- Baseline risk of relapse

As reported in the Evidence review C, appendix J, the risk of relapse in people with depression that is in remission is dependent on time, following a Weibull distribution in which the relapse rate is proportional to a power of time. People have a higher risk of relapse in the early years following remission, and this risk is reduced with every year they remain in remission; the cumulative hazard rate for the Weibull distribution is given by the following mathematical formula:

$$H(t) = \lambda t^{\gamma}$$

where lambda (λ) and gamma (γ) are the scale and shape parameters of the distribution, respectively.

Moreover, there is evidence that the risk of relapse increases with the number of previous episodes.

A literature review and synthesis of data from cohort studies following people who remitted from a single (first) episode of depression (Eaton 2008; Mattisson 2007) determined the parameters of the Weibull distribution characterising the baseline risk of relapse after remission of a single episode over time. These parameters are shown in Table 80. Details of the literature review and data synethis are provided in Evidence review C, appendix J. Their use in the model allowed estimation of the baseline risk of relapse in people in the remission state according to the time they remained in the state (one or two years).

Table 80. Parameters of the Weibull distribution of risk of relapse over time, in people who are in remission following a single (first) episode

Parameter	Mean	SD	Median	95% Credible intervals
Lambda	0.09	0.01	0.09	0.07 to 0.12
Gamma	0.63	0.06	0.63	0.52 to 0.75

The increase in the risk of relapse for every additional depressive episode was considered by applying the hazard ratio of relapse with every additional episode as estimated by Kessing 1999, who reported the results of a case register study that included all hospital admissions with primary affective disorder in Denmark during 1971-1993. A total of 7,925 people with unipolar depression were included in the study. The authors reported that the risk of relapse increased with every new episode by a mean hazard ratio of 1.15 (95% CI 1.11-1.18). Use of this ratio allowed estimation of the baseline relapse risk for people with more severe depression who, following successful treatment, recovered from their third episode.

- Risk of relapse associated with interventions aiming at relapse prevention

The effect of relapse preventive treatments in people who completed acute treatment and moved to the remission state in the Markov component of the model was expressed as a hazard ratio versus baseline, and was applied onto the baseline risk of relapse over the first 2 years of the Markov model. The hazard ratios of maintenance treatments versus baseline (GP care, expressed by placebo trial arms) were derived from the NMAs conducted for this guideline to inform the relapse prevention guideline economic models (see details on Evidence review C, appendix J), as described below.

The hazard ratios versus GP care that were utilised in the Markov component of this economic analysis for cost-effective maintenance treatments were obtained from the relapse

prevention model conducted for this guideline and are presented in Table 81. Hazard ratios of relapse preventive interventions were determined by the type of acute treatment (pharmacological, psychological, physical or combined) people received, that led to response of their depressive episode, as estimated in the Evidence review C, appendix J. For people who received acute combined treatment in the economic analysis, efficacy data on relapse prevention treatment were received from the NMA of treatments for people who responded to acute pharmacological treatment, due to lack of relevant data on people who responded to acute combined treatment. For people who received acute physical treatment in the economic analysis, efficacy data on relapse prevention treatment were received from the NMA of treatments for people who responded to acute psychological treatment, due to lack of relevant data on people who responded to acute physical treatment. The hazard ratios of 4 sessions of psychological interventions received as maintenance treatment were assumed to equal the hazard ratios of maintenance individual CT/CBT, in the guideline relapse prevention NMAs.

Table 81. Hazard ratios of cost-effective maintenance treatments received by people with more severe depression who responded to treatment - Results of the NMAs conducted to inform the guideline economic analyses of interventions aiming at relapse prevention in people whose depression has responded to treatment (Evidence review C, appendix J)

Intervention	Mean hazard ratio versus placebo (95% credible intervals)
Adults whose (more severe) depression responded to acute pharmacological treatment [data also applied to adults whose depression responded to acute combined treatment]	
Maintenance AD treatment	0.49 (0.44 to 0.55)
MBCT + GP care (AD drug tapering)	0.46 (0.31 to 0.65)
Individual CT/CBT + GP care (AD drug tapering)	0.50 (0.30 to 0.79)
Adults whose (more severe) depression responded to acute psychological treatment [data also applied to adults whose depression responded to phsycial treatment]	
4 sessions of intervention received as acute treatment (assumed to equal effect of maintenance individual CT/CBT)	0.67 (0.31 to 1.26)
MBCT	0.90 (0.30 to 2.11)
Group CT/CBT	1.03 (0.30 to 2.59)

AD: antidepressant; CBT: cognitive behavioural therapy; CT: cognitive therapy; MBCT: mindfulness based cognitive therapy

Probability of remission in the Markov component of the economic model

The probability of remission in people who are in the depressive episode state in the Markov component of the economic model was determined by the time spent in the depressive episode state. As discussed earlier, the probability of remission in people with depression follows a Weibull distribution in which the remission rate is proportional to a power of time. People have a higher annual probability of remission in the early years following initiation of the depressive episode, and this probability is reduced with every year they remain in the episode.

A literature review and synthesis of data from cohort studies following people with depression determined the parameters of the Weibull distribution characterising the probability of remission over time, as it has been shown in Table 78. Their use in the model allowed estimation of the risk of remission in people in the depressive episode state according to the time they remained in the state (one or two years).

These parameters were estimated using data from studies on cohorts with depression followed over long periods of time, irrespective of their level of symptom severity.

In order to estimate the Weibull parameters of remission for adults with less severe depression and adults with more severe depression, data were taken from Simon 1999, as discussed earlier. The probability of remission at 12 months by baseline symptom severity reported in this study was used to estimate lambda parameters for the underlying distribution at each level of symptom severity. The shape parameter gamma that was estimated for recovery from synthesis of cohort studies was assumed to apply across all symptom severity levels. This way a Weibull distribution for recovery was determined for each level of symptom severity; details of the distribution for each level of recovery have been shown in Table 79.

The probability of remission for adults with less severe depression in their first and second year in the depressive episode state of the Markov model was estimated using the Weibull parameters for people with mild depression shown in Table 79. The probability of remission for adults with more severe depression in their first and second year in the depressive episode state of the Markov model was estimated as an average of respective probabilities estimated for people with moderate and severe depression using the Weibull parameters relevant to each population shown in the same table.

People who entered the Markov component via the depressive state were already in non-remission for 12 weeks and therefore their probability of remission in the first and second year following entrance to the Markov depressive state corresponded to model time points between 12-64 weeks and 64-116 weeks, respectively. This was accounted for in the estimation of probability of remission for this sub-group in the economic analysis.

Probability of development of side effects from antidepressant treatment

Treatment with antidepressants is associated with the development of various side effects. These can be serious, including death, attempted suicide or self-harm, falls, fractures, stroke or transient ischaemic attack, epilepsy/seizures, myocardial infarction, hyponatraemia and upper gastrointestinal bleeding (Coupland 2011; Coupland 2018; Jakobsen 2017) or less serious but more common, such as headaches, nausea and other gastrointestinal symptoms, dizziness, agitation, sedation, sexual dysfunction, tremor, sweating, fatigue, dry mouth, sleepiness during the day or sleeplessness, weight gain and arrhythmia (Anderson 2012, Bet 2013; Jakobseon 2017; Uher 2009).

Serious side effects from antidepressants are costly to treat and are likely to reduce the HRQoL of people who experience them more significantly compared with less serious side effects. However, they do not occur frequently. Coupland 2011 investigated the association between antidepressant treatment and the risk of several potential adverse outcomes in older people with depression, in a retrospective cohort study that utilised data from 60,746 people aged 65 and over diagnosed as having a new episode of depression, obtained across 570 general practices in the UK between 1996 and 2008. The authors reported that SSRIs were associated with the highest adjusted hazard ratios for falls (1.66, 95%; CIs 1.58 to 1.73) and hyponatraemia (1.52; 95% CIs 1.33 to 1.75) compared with when antidepressants were not being used, while a group of ‘other antidepressants’ defined according to the British National Formulary, which included mirtazapine and venlafaxine, among others, was associated with the highest adjusted hazard ratios for all-cause mortality (1.66; 95% CIs 1.56 to 1.77), attempted suicide or self-harm (5.16; 95% CIs 3.90 to 6.83), stroke/transient ischaemic attack (1.37; 95% CIs 1.22 to 1.55), fracture (1.64; 95% CIs 1.46 to 1.84), and epilepsy/seizures (2.24; 95% CIs 1.60 to 3.15), compared with when antidepressants were not being used. However, for most of these side effects, with the exception of all-cause mortality, the difference in absolute risks between people who received antidepressants and those who were not taking antidepressants during the assessment period was small (lower than 1%) with few exceptions: considering the drugs and classes that were included in the guideline economic analysis, for SSRIs, the absolute increase in risk of falls compared with people who were not taking antidepressants was 2.21%; for mirtazapine, the absolute increase in risk of attempted suicide or self-harm compared with people who did not take

antidepressants was 1.31%. It is noted that these data were derived from older adults with depression, who are likely to have a higher baseline risk for these events compared with younger populations. Therefore, the absolute increase in risk for any of these events in the study population, between those taking antidepressants and those not taking antidepressants, is expected to be lower than that observed between respective groups in older populations.

Similarly, Coupland 2018 investigated the association between antidepressant treatment and the risk of several potential adverse outcomes in 238,963 adults aged 20-64 years registered with general practices across the UK, who had a first diagnosis of depression between 2000 and 2011. Relative to other antidepressant treatment classes, SSRIs were associated with the highest adjusted hazard ratios for falls (1.48, 95%; CIs 1.39 to 1.59), and fracture (1.30; 95% CIs 1.21 to 1.39), compared with when antidepressants were not being used, while TCAs were associated with the highest adjusted hazard ratios for upper gastrointestinal bleeding (1.43; 95% CIs 1.13 to 1.81) and all cause mortality (1.92; 95% CIs 1.68 to 2.19). Other antidepressants were associated with the highest adjusted hazard ratio for adverse drug reaction (2.81; 95% CIs 2.11 to 3.75). Again, the difference in absolute risks between people who received antidepressants and those who were not receiving antidepressants during the assessment period was very small (e.g. difference 0.001% in falls between people under SSRIs and those under no antidepressant treatment; 0.002% in fractures between people under other antidepressants and those under no antidepressant treatment). Therefore, the absolute increase in risk for any of these events in the study population, between those taking antidepressants and those not taking antidepressants is very small and expected to have a negligible impact on costs and HRQoL.

Jakobsen 2017 conducted a systematic review and meta-analysis to assess the effects (including adverse events) of SSRIs versus placebo, 'active' placebo, or no intervention in adult participants with major depressive disorder. The authors reported that SSRIs significantly increased the risks of serious adverse events (odds ratio 1.37; 95% CI 1.08 to 1.75) corresponding to 31/1000 SSRI participants experiencing a serious adverse event compared with 22/1000 control participants (that is a 0.9% difference).

Bet 2013 assessed the risk of common side effects in 846 adults with depression and/or anxiety who received antidepressant monotherapy on 927 occassions, recruited from primary care and specialist mental health settings in the Netherlands. Participants were asked to fill in a short 12-question antidepressant side effect checklist, to self-report patient-perceived common side effects related to their antidepressant therapy. Common side effects included sleeplessness, sleepiness during the day, restlessness, muscle spasms and twitching, dry mouth, profuse sweating, sexual dysfunction, nausea, constipation, diarrhea, weight gain and dizziness. Large percentages of participants in the study reported at least 1 side effect as shown in Table 82.

Table 82. Percentages of people under antidepressant medication reporting zero, 1-2 or 3 side effects and above (from Bet 2013)

Antidepressant	N	% reporting zero side effects	% reporting 1-2 side effects	% reporting ≥ 3 side effects
SSRI	584	36%	33%	31%
TCA	97	28%	33%	39%
Venlafaxine	145	27%	37%	36%
Mirtazapine	58	36%	40%	24%
Other	19	47%	26%	26%

However, it is not known whether these common side effects have a significant impact on HRQoL or lead to the use of additional healthcare resources, e.g. trigger extra GP visits.

Moreover, as this was an uncontrolled study, it cannot be determined whether the side effects reported were indeed a result of antidepressant use.

Cascade 2009 conducted a cross-sectional study on approximately 700 patients receiving SSRI medication, to explore the prevalence of side effects and their impact on HRQoL and healthcare service contacts. The study reported that 38% of study participants experienced a side effect. However, only 25% of the side effects were considered “very bothersome” or “extremely bothersome” by the respondents. Moreover, regardless of how bothersome the side effects were, only 40% of SSRI users mentioned the side effects to their prescribing physicians.

Anderson 2012 estimated the prevalence of 5 common side effects that included headaches, nausea or vomiting, agitation, sedation and sexual dysfunction associated with treatment with antidepressants, by undertaking a retrospective analysis of data derived from a large USA managed care claims form on 40,017 people aged 13 years and above, of whom 36,400 were adults aged 19 years and above, who were newly diagnosed with depression and were initiated on antidepressant monotherapy between 1998 and 2008. Antidepressant groups included, among others, SSRIs, SNRIs, TCAs, phenylpiperazines (which, in 84% of cases were represented by trazodone) and tetracyclic antidepressants (which, in 99% of cases, were represented by mirtazapine). The authors reported that the most common side effect of those assessed was headaches, followed by nausea. The prevalence, rates of experiencing at least one of the 5 common side effects considered in the study, and the estimated length of time of people experiending at least one common side effect for the antidepressants of interest in the economic analysis are shown in Table 83.

Table 83. Prevalence, rates and length of time experiencing at least one common side effect of antidepressants in adults with depression (from Anderson 2012)

Antidepressant	N	% developing ≥ 1 side effect	Rate[1] experiencing ≥ 1 side effect	Length of time with ≥ 1 side effect (years)
SSRI	23,620	7.0%	0.117	1.68
SNRI	4,762	9.2%	0.150	1.63
TCA	776	6.7%	0.152	2.26
Trazodone	1,200	4.7%	0.182	3.84
Mirtazapine	901	6.0%	0.163	2.72

1 per person-years

The committee considered the available evidence and agreed that, although side effects are common, only a proportion of them have a measurable impact on HRQoL and result in an increase in healthcare resource use, and have thus an impact on the cost effectiveness of antidepressant treatments. This is supported by data reported in Cascade 2009. They also expressed the view that studies asking specifically participants to self-report the presence of side effects choosing from a side-effect checklist (such as the Bet 2013 study) tend to overestimate the prevalence of side effects in the study population, in particular as these use uncontrolled study designs and the causality between the antidepressant use and the reported side effects is not established. Using data from Bet 2013 (or other similar study designs) to inform the risk of side effects for pharmacological treatment options in the economic model would likely overestimate the impact of side effects on the relative cost-effectiveness between pharmacological and non-pharmacological treatments, especially as psychological treatments were assumed to have a zero risk of side effects.

On the other hand, the committee expressed the view that claims for side effects that come up spontaneously, via healthcare service contacts, such as those reported in Anderson 2012, are more representative of the risk of side effects that have an impact on HRQoL and healthcare costs. Therefore, the committee agreed to use the data reported in Anderson 2012 in order to inform the base-case economic analysis on the risk of side effects from

antidepressant medication use. The economic model took into account the percentage of people experiencing at least 1 side effect for each antidepressant of interest (and their combinations with psychological or physical treatment), and the length of time those people spent experiencing at least 1 side effect. This equalled the duration of the model (2.25 years) for people receiving TCAs, trazodone and mirtazapine. People receiving SSRIs or SNRIs who experienced at least 1 common side effect did so for the first 12 weeks and the 1st year of maintenance treatment [where relevant], and for 0.43 and 0.38, respectively, of their time in 2nd year of maintenance treatment. The model considered the impact of common side effects on treatment costs and people's HRQoL.

After consideration of all available data on the risk of side effects from antidepressant medication use, in a sensitivity analysis, the committee advised that a risk of side effects of 40% be explored, as the higher end of the risk that might have an impact on HRQoL and management costs.

No side effects were considered for people receiving non-pharmacological interventions; however, people receiving non-pharmacological interventions are also expected to experience a range of events such as headaches, nausea or vomiting, etc. Anderson 2012 was an uncontrolled study and did not examine the rate of side effects that were attributable to drugs. Therefore, in this aspect, the economic analysis may have overestimated the impact of common side effects from antidepressants relative to other treatments and thus underestimated their relative cost effectiveness.

The economic model did not incorporate the impact of less common but more severe side effects on costs and people's HRQoL, as this would require most complex modelling and detailed data on the course and management of these side effects. However, omission of these severe side effects is not expected to have considerably affected the results of the economic analysis, due to their low incidence in the study population. Nevertheless, omission of less common but severe side effects from the economic analysis may have potentially somewhat overestimated the cost effectiveness of pharmacological and combined treatments regarding the risk of severe side effects associated with drugs.

Mortality

Depression is associated with an increased risk of mortality relative to the general population. A comprehensive systematic review of 293 studies that assessed the increased risk of people with depression relative to non-depressed individuals, which included 1,813,733 participants (135,007 depressed and 1,678,726 non-depressed) reported a risk ratio of mortality in depressed relative to non-depressed participants of 1.64 (95% CI 1.56 to 1.76). After adjustment for publication bias, the overall risk ratio was reduced to 1.52 (95% CI 1.45 to 1.59) (Cuijpers 2014).

The risk of mortality for people with a new episode of depression was not considered in the decision-tree part of the model (12 weeks), because death (mainly due to suicide) is a rare outcome in RCTs of acute treatments for depression, and no substantial differential data on mortality or, specifically, on the risk of suicide between treatments assessed in the economic analysis are available.

In the Markov component of the model, the adjusted risk ratio of mortality in depressed relative to non-depressed participants (Cuijpers 2014) was applied onto general mortality statistics for the UK population (Office for National Statistics 2020), to estimate the absolute annual mortality risk in people experiencing a depressive episode relative to people not experiencing a depressive episode within each cycle of the model. People with a depressive episode were assumed to be at increased mortality risk due to depression only in the years they experienced a depressive episode. The same mortality risk was assumed for both men and women experiencing a relapse, as no gender-specific data were reported in the study.

People not experiencing a depressive episode in each model cycle were assumed to be subject to the mortality risk of the general UK population.

Utility data and estimation of quality adjusted life years (QALYs)

In order to express outcomes in the form of QALYs, the health states of the economic model (remission, response not reaching remission, no response or relapse) need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration.

The systematic review of utility data on depression-related heath states identified 7 studies that reported utility data corresponding to depression-related health states, which were derived from EQ-5D measurements on adults with depression valued by the general UK population (Kaltenthaler 2006; Koeser 2015; Kolovos 2017; Mann 2009; Sapin 2004; Sobocki 2006 & 2007; Soini 2017). Four of the studies analysed EQ-5D data obtained from adults with depression or common mental health problems participating in RCTs, 3 of which were conducted in the UK (Kaltenthaler 2006, Mann 2009, Koeser 2015) and one in various European countries, including the UK (Soini 2017). One study reported findings from an individual patient-level meta-analysis of EQ-5D data from 1629 adults mainly with depression (although a small proportion might have had anxiety and/or other common mental health problems) that had participated in 10 RCTs of interventions or services for people with depression in the Netherlands (Kolovos 2017). The other two studies analysed naturalistic primary care EQ-5D data from adults with depression in France (Sapin 2004) and in Sweden (Sobocki 2006 & 2007). All studies reported utility values associated with severity of depression (mild, moderate or severe) and/or states of depression relating to treatment response (response, remission, no response) and were thus relevant to the health states considered in economic modelling conducted for this guideline. All studies defined health states using validated measures of depressive symptoms, such as the BDI, the HAMD-17, the PHQ-9, the MADRS, the CGI, the CES-D, the HADS-D or the IDS-SR (inventory of depressive symptomatology self-report).

An overview of the study characteristics, the methods used to define health states, and the health-state utility values reported by each of the studies is provided in Table 84.

Table 84. Summary of available EQ-5D derived health-state utility data for depression (UK tariff)

Study	Definition of health states	Health state / severity	N	Mean (SD or 95% CI)
Kaltenthaler 2006	Analysis of EQ-5D and CORE-OM data obtained from 62 people with common mental health problems participating in a multi-centre RCT of supervised self-help CBT in the UK (Richards 2003). CORE-OM data were first mapped onto the BDI, which was used to categorise people into 3 groups of mild to moderate, moderate to severe and severe depression. BDI cut-off scores used for categorisation were not reported. EQ-5D utility value for no depression obtained from age- and gender-matched normal population in the UK (Kind 1999).	No depression Mild to moderate Moderate to severe Severe	NA NR NR NR	0.88 (0.22) 0.78 (0.20) 0.58 (0.31) 0.38 (0.32)
Koeser 2015	Analysis of EQ-5D and HAMD17 data obtained from people with recurrent depression in full or partial remission participating in a RCT of MBCT in the UK (N=123) (Kuyken 2008). Definition of health states by HAMD scores: remission ≤ 7; response 8-14; no response ≥ 15	Remission Response No response	NR NR NR	0.80 (0.02) 0.62 (0.04) 0.48 (0.05)
Kolovos 2017	Analysis of EQ-5D and symptom scale score data (CES-D or MADRS or PHQ-9 or IDS-SR or HADS-D) from 1629 adults mainly with depression (although a small proportion might have had anxiety and/or other common mental health problems) that had participated in 10 RCTs of interventions or services for people with depression in the Netherlands; 4979 observations considered. Definition of health states by CES-D score: remission 0-15; minor 16-19; mild 20-25; moderate 26-30; severe 31-60; definition of health states by MADRS score: remission 0-8; minor 9-18; mild 19-26; moderate 27-34; severe 35-60; definition of health states by PHQ-9 score: remission 0-4; minor 5-9; mild 10-14; moderate 15-19; severe 20-27; definition of health states by IDS-SR score: remission 0-13; minor 14-25; mild 26-38; moderate 39-48; severe 49-84; definition of health states by HADS-D score: remission 0-7; minor 8-13; mild 14-19; moderate 20-25; severe 26-52.	Minor Mild Moderate Severe Remission	NR NR NR NR NR	0.62 (0.58-0.65) 0.57 (0.54-0.61) 0.52 (0.49-0.56) 0.39 (0.35-0.43) 0.70 (0.67-0.73)
Mann 2009	Analysis of EQ-5D and PHQ-9 data collected from 114 people with depression participating in a cluster RCT of collaborative care across 19 UK primary care practices based in urban and rural communities (Richards 2008). Definition of health states by PHQ-9 score: mild 5-9; moderate 10-14; moderately severe 15-19; severe 20-27	Mild Moderate Moderate to severe Severe	10 24 39 35	0.65 (0.23) 0.66 (0.21) 0.56 (0.27) 0.34 (0.29)
Sapin 2004	Analysis of EQ-5D and MADRS data collected from 250 people with major depression recruited from 95 French primary care practices for inclusion in an 8-week follow-up cohort. Definition of health states by MADRS score: remission MADRS ≤ 12; response at least 50% reduction in the	Response – remission Response – no remission No response	144 34 46	0.85 (0.13) 0.72 (0.20) 0.58 (0.28)

Study	Definition of health states	Health state / severity	N	Mean (SD or 95% CI)
	MADRS baseline score over 8 weeks. Baseline mean MADRS score 32.7 (SD 7.7)	Baseline	250	0.33 (0.25)
Sobocki 2006 & 2007	Analysis of EQ-5D and CGI-S and CGI-I data collected from 447 adults with depression enrolled in a naturalistic longitudinal observational 6-month study conducted in 56 primary care practices in 5 regions of Sweden. People who started a new or changed antidepressant treatment were eligible for inclusion. Definition of health states by CGI-S score: mild 2-3; moderate 4; severe 5-7; remission 'much or very much improved' score (1-2) combined with clinical judgement	Mild Moderate Severe Remission No remission	110 268 69 207 191	0.60 (0.54 to 0.65) 0.46 (0.30 to 0.48) 0.27 (0.21 to 0.34) 0.81 (0.77 to 0.83) 0.57 (0.52 to 0.60)
Soini 2017	Analysis of EQ-5D, MADRS and HAMD data obtained from people with depression and an inadequate response to a SSRI/SNRI participating in a RCT of vortioxetine versus agomelative in a multi-national RCT conducted in inpatient and outpatient settings in 14 European countries, including the UK (N=501) (Montgomery 2014). Mean MADRS score at baseline: 28.9; remission defined as MADRS score ≤10 or HAMD score ≤7	Baseline Remission No remission	NR NR NR	0.54 0.85 0.62

N: number of participants who provided ratings on each state
BDI: Beck Depression Inventory; CBT: cognitive behavioural therapy; CES-D: Center for Epidemiologic Studies Depression Scale; CGI-I: Clinical Global Impression – Improvement scale; CGI-S: Clinical Global Impression – Severity scale; CI: confidence intervals; CORE-OM: Clinical Outcomes in Routine Evaluation – Outcome Measure); HADS-D: Hospital Anxiety and Depression Scale Depression subscale; HAMD: Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Ssymptomatology Self-Report; MADRS: Montgomery-Asberg Depression Rating Scale; MBCT: Mindfullness Based Cognitive Therapy; NR: not reported; PHQ: Patient Health Questionnaire; SNRI: Serotonin–Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; RCT: randomised controlled trial; SD: standard deviation

All reported utility data comply with the NICE criteria on selection of utility data for use in NICE economic evaluations (NICE 2013). The data from Kaltenthaler 2006 were derived following mapping of CORE-OM data onto BDI data; however, the BDI cut-off scores used to determine the health states by depressive symptom severity were not reported, and therefore it is not clear the exact level of symptom severity the resulting utility scores correspond to. All other studies provided details on the scale cut-off scores used to determine the depression-related health states by severity or by response to treatment. Mann 2009 used the original PHQ-9 cut-off scores to determine severity levels of depression. However, it is noted that a PHQ-9 score of 5-9, which corresponded to the state of mild depression according to the PHQ-9 manual, is also below the cut-off point for clinically detected depression (Gilbody 2007a & 2007b). Kolovos 2017 used a number of different scales to determine severity levels of depression in their study sample, with cut-off scores being determined based on the literature and not necessarily to scale manuals.

The economic analysis utilised a combination of data from Sapin 2004 and Sobocki 2006 & 2007 for the states of acute treatment, corresponding to the decision-tree component of the model. This was decided because these two studies provided data for all states included in the model, i.e. less and more severe depression at initiation of treatment or following a relapse, remission, response not reaching remission, and no or inadequate response, and were based on larger study samples compared with other studies providing utility data for similar health states, together with Kolovos 2017 and Soini 2017. It is noted though, that remission in Sobocki 2006 & 2007 was defined as an improved or very much improved score on the CGI-Improvement scale, combined with a clinical judgement by the treating doctor of being in full remission. It is acknowledged that this definition of remission may actually include response to treatment not reaching full remission.

For less severe depression the utility value corresponding to mild depression (0.60) was used, because the study population with less severe depression includes populations with sub-threshold and mild depression. This value for less severe depression (0.60) is consistent with the average of the utility values for minor (0.62) and mild (0.57) depression reported by Kolovos 2017.

For more severe depression, a weighted average of the utility of moderate and severe depression of 0.42 (obtained from Sobocki 2006 & 2007) was used. This estimated value for more severe depression (0.42) is somewhat lower but broadly consistent with the average of the utility values for moderate (0.52) and severe (0.39) depression reported by Kolovos 2017.

For people reaching remission and those with more severe depression responding to acute treatment without reaching remission (i.e. at the end of the decision-tree component of the model) the reported values of 0.85 and 0.72 from Sapin 2004 were used, respectively. It is noted that the value of 0.85 for remission is supported by Soini 2017. On the other hand, both values of remission and response without remission reported in Sapin 2004 are higher than the utility value of remission of 0.70 reported by Kolovos 2017. People with no or inadequate response to treatment were assumed to remain in the same state of less severe (0.60) or more severe (0.42) depression.

For the Markov component of the model, the slightly more conservative value of 0.81, reported by Sobocki 2006 & 2007, rather than the value of 0.85, reported by Sapin 2004 was used for people in remission, to reflect the fact that some people may not be in full remission for the whole model cycle, but may experience some symptoms which, nevertheless, are not adequate to indicate relapse. The values of 0.60 and 0.42 were used for people in the depressive less severe and more severe states, respectively, of the Markov component of the model.

In sensitivity analysis, the values of 0.80 (Koeser 2015) and 0.70 (Kolovos 2017) for remission and 0.62 for response not reaching remission (Koeser 2015) were tested as a

more conservative scenario. It is noted that Soini 2017 also reported a value of 0.62 for people not reaching remission. Moreover, in another scenario, the values of 0.65 and 0.56, reported by Mann 2009 for mild and moderate-to-severe depression were attached to the states of less severe and more severe depression, respectively.

Changes in utility between baseline and endpoint of the decision-tree part of the model were assumed to occur linearly over time.

According to the committee's expert opinion, an average depressive episode lasts 6 months. This estimate is supported by data from a prospective study on 250 adults with a newly originated (first or recurrent) major depressive episode, drawn from a prospective epidemiological Dutch survey on 7,046 people in the general population (Spijker 2002). According to this study, the mean duration of a recurrent episode was 6.1 months (95% CI 4.7-7.5). The economic model assumed that people in the Markov component of the model experiencing a depressive episode that resolved in the next year (i.e. people who spent only a year in the depressive episode and then moved to the remission state in the next cycle), experienced a reduction in their HRQoL for 6 months out of the 12 months of the cycle they remained in the 'depressive' state. Thus, people relapsing to depressive episodes that lasted only for one year were assumed to have the utility of remission for 6 months and the utility of depression (less or more severe) for another 6 months. However, people whose depressive episode was expected to last for 2 cycles (years) or more, were attached the utility of depression over the number of years (1 or 2) they remained in the depressive episode except their final year in the episode, in which they were assumed to have the utility of depression for 6 months and the utility of remission for another 6 months.

Side effects from medication are expected to result in a reduction in utility scores of adults with depression. Sullivan 2004 applied regression analysis on EQ-5D data (UK tariffs) obtained from participants in the 2000 national USA Medical Expenditure Panel Survey to derive age-adjusted utility values for health states associated with depression and with side effects of antidepressants. Health states were defined based on descriptions in the International Classification of Diseases (9th Edition) (ICD-9) and the Clinical Classification Categories (CCC) (clinically homogenous groupings of ICD-9 codes derived by the Agency for Healthcare Research and Quality). Table 85 shows the health states determined by Sullivan 2004 and the corresponding utility values obtained from regression analysis of EQ-5D data. The mean utility decrements due to side effects from antidepressants ranged from -0.044 (diarrhoea) to -0.129 (excitation, insomnia and anxiety), with a mean decrement of -0.087. This mean utility decrement was used in the economic model for people who discontinued treatment due to intolerable side effects, as no specific information on the type and frequency of side effects that led to discontinuation was available across RCTs; it was applied over 5 weeks, based on the committee's advice on the duration of reduction in HRQoL due to intolerable side effects. This utility decrement was also applied to the proportion of people who completed antidepressant treatment and experienced tolerable side effects, over the whole period of antidepressant treatment, i.e. over 12 weeks (acute antidepressant treatment) and the following 2 years (only in those receiving maintenance antidepressant treatment).

Table 85. Summary of EQ-5D derived health-state utility data for side effects from antidepressants (UK tariff)

Study	Definition of health states	Health state	Mean (95% CI)
Sullivan 2004	Censored least absolute deviations (CLAD) regression analysis of EQ-5D data from the 2000 national US Medical Expenditure Panel Survey (MEPS) [http://meps.ahrq.gov/mepsweb/] Definitions of health states Gastrointestinal symptoms (GI): average Diarrhoea: clinical classification categories (CCC) - Agency for Healthcare Research and Quality): 144 regional enteritis Dyspepsia: CCC 138 oesophageal disorders Nausea & constipation: assumed average of GI Sexual: ICD-9 302 sexual disorders Excitation: average Insomnia: assumed equal to anxiety Anxiety: CCC 072 anxiety, somatoform, dissociative disorders Headache: CCC 084 headache Drowsiness & other: assumed average of all side effects Untreated depression ICD-9 311 depressive disorder; CLAD 25% Treated depression: ICD-9 311 depressive disorder; CLAD 75%; baseline utility estimate (not a decrement)	GI symptoms Diarrhoea Dyspepsia Nausea Constipation Sexual Excitation Insomnia Anxiety Headache Drowsiness Other Untreated depression Treated depression	-0.065 (-0.082 to -0.049) -0.044 (-0.056 to -0.034) -0.086 (-0.109 to -0.065) -0.065 (-0.082 to -0.049) -0.065 (-0.082 to -0.049) -0.049 (-0.062 to -0.037) -0.129 (-0.162 to -0.098) -0.129 (-0.162 to -0.098) -0.129 (-0.162 to -0.098) -0.115 (-0.144 to -0.087) -0.085 (-0.107 to -0.065) -0.085 (-0.107 to -0.065) -0.268 (-0.341 to -0.205) 0.848 (0.514 to 0.971)

Intervention resource use and costs

Intervention costs were estimated by combining resource use associated with each intervention with appropriate unit costs (drug acquisition costs, healthcare professional unit costs, and costs of equipment and infrastructure, as relevant).

Pharmacological interventions

Pharmacological intervention costs consisted of drug acquisition and GP visit costs. In addition to pharmacological treatment, the model also considered GP care (reflected in RCT arms of the reference treatment, which was TAU for less severe depression and placebo for more severe depression), which comprised GP visits only.

The average daily dosage for each drug was determined according to optimal clinical practice (British National Formulary 2021), following confirmation by the committee's expert opinion to reflect routine clinical practice in the NHS, and was consistent with dosages reported in the RCTs that were included in the RCTs of pharmacological interventions included in the NMA.

Titration was not explicitly considered in the model; however, in each cohort different percentages of people were allowed to receive different drug daily doses to reflect that some people require titration to a higher dose to achieve optimal intervention effects.

Acute pharmacological treatment was administered over 12 weeks. After this period, adults with less severe depression who achieved remission received their drug for another year and had it gradually discontinued (tapered) towards the end of this year; this was modelled as a linear reduction of the drug acquisition cost (from optimal dose to zero) over a period of three months (according to routine clinical practice, as advised by the committee) towards the end of year 1 into the remission state of the Markov model. Adults with more severe depression who responded to pharmacological or combined treatment either received maintenance pharmacological treatment with the same drug over 2 years (with gradual discontinuation (tapering) of the drug at the end of year 2 into the Markov model, or received psychological treatment combined with 1 year continuation of the pharmacological treatment and gradual discontinuation (tapering) of the drug at the end of year 1 into the Markov model. Tapering was modelled as a linear reduction in the drug acquisition cost at the end of year 1 or 2 into the remission state of the Markov model, as relevant, and over a period of three months, according to routine clinical practice, as advised by the committee.

Provision of acute pharmacological treatment involved 4 GP visits. Four GP visits were also assumed for people under GP care. These resource use estimates were based on the committee's expert advice; they represent UK optimal routine clinical practice but may be lower than some of the descriptions of medical resource use in pharmacological trial protocols, where resource use is more intensive than clinical practice.

People who received TCAs were assumed to receive a liver function test (LFT) at treatment initiation, and an electrocardiogram (ECG) at treatment initiation and at 6 weeks, according to optimal clinical practice, as advised by the committee.

The drug acquisition costs and the GP unit cost were taken from national sources (Curtis 2020, NHS Business Services Authority 2021). The reported GP unit cost included remuneration, direct care staff costs and other practice expenses, practice capital costs and qualification costs. The latter represented the investment costs of pre-registration and postgraduate medical education, annuitised over the expected working life of a GP; ongoing training costs were not considered due to lack of available information. The unit cost per patient contact was estimated taking into account the GPs' working time as well as the ratio of direct (surgeries, clinics, telephone consultations & home visits) to indirect (referral letters, arranging admissions) patient care, and time spent on general administration. The LFT unit

cost was taken from Akhtar 2014. The ECG cost comprised the cost of the machine and disposables, obtained from National Clinical Guidelines Centre 2016, and 20 minutes of a practice nurse's (Band 5) time. The unit cost for a practice nurse was obtained from Curtis 2020; the cost included wages/salary, salary oncosts, capital and other overheads, In estimating the unit cost per hour of client contact, the ratio of direct (face-to-face) to indirect time (reflecting time for preparation of therapeutic sessions and other administrative tasks) of the practice nurse was also taken into account.

Intervention costs of acute pharmacological treatment and GP care are shown in Table 86.

Table 86. Intervention costs of pharmacological interventions for the acute treatment of adults with a new episode of depression considered in the guideline economic analysis (2020 prices)

Drug	Mean daily dosage	Drug acquisition cost[1]	12-week drug cost	Total intervention cost (drug, GP[2], testing[3]) – acute treatment
Sertraline	50% 50mg; 25% 100mg; 15% 150mg; 10% 200mg	50mg, 28 tab, £2.30 100mg, 28 tab, £3.23	£10.30	£166.30
Escitalopram	80% 10mg; 20% 20mg	10mg, 28 tab, £1.40 20mg, 28 tab, £1.55	£4.29	£160.29
Lofepramine	80% 140mg; 20% 210mg	70mg, 56 tab, £16.95	£55.94	£255.83
Duloxetine	80% 60mg; 20% 120mg	60mg, 28 caps, £3.38	£12.17	£168.17
Mirtazapine	30% 15mg; 50% 30mg; 20% 45mg	15mg, 28 tab, £1.73 30mg, 28 tab, £1.74 45mg, 28 tab, £2.11	£5.43	£161.43
Trazodone	80% 150mg; 20% 300mg	150mg, 28 tabs, £2.40	£8.64	£164.64
GP care	Non-applicable	Non-applicable	Non-applicable	£156.00

1 NHS Business and Services Authority 2021
2 GP cost includes 4 visits for active acute pharmacological treatment and 4 visits for GP care; GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020)
3 The cost of lofepramine includes the additional costs of liver function test (LFT) at treatment initiation and electrocardiogram (ECG) at treatment initiation and at 6 weeks. LFT unit cost £3.07 (Akhtar 2014). ECG unit cost £20.41, comprising £3.28 for machine and disposables (National Clinical Guidelines Centre 2016) and £17.13 for 20 minutes of a practice nurse's (Band 5) time (Curtis 2020).

Psychological interventions

Resource use estimates of each psychological therapy in terms of number and duration of sessions and also number of therapists and participants in the case of group interventions were determined by resource use data described in respective RCTs that were included in the NMAs that informed the economic analysis, modified by the committee to represent routine clinical practice in the UK. For most psychological interventions, resource use differed between less severe and more severe depression, according to reported data in the RCTs (see Appendix N) and the committee's expert opinion.

High intensity individual psychological interventions were assumed to be delivered by agenda for change (AfC) band 7 high intensity therapists with a range of background qualifications, including clinical psychologists, counsellors, therapists that started their career as psychological well-being practitioners (PWPs), nurses (the latter is more often seen in secondary care), etc. (NHS England and Health Education England 2016a). High-intensity

interventions delivered in groups, such as group CBT, group BA and group MBCT were assumed to be delivered by one AfC band 7 high intensity therapist, who led and actively facilitated the delivery of the therapy, supported by one AfC band 6 therapist, who observed the delivery of the intervention according to optimal practice, who might be, for example, a PWP who had received additional Improving Access to Psychological Therapies (IAPT) training or a trainee clinical psychologist. Low intensity psychological interventions (self-help with support and individual problem solving) were assumed to be delivered by an AfC band 5 low intensity therapist, who in IAPT services is usually a PWP. These assumptions were based on the committee's expert advice regarding the optimal delivery of psychological interventions in routine clinical practice (predominantly IAPT services), although it was acknowledged that there may be some further variation in the types of therapists delivering psychological interventions across different settings in the UK.

Therapist unit costs were estimated using a combination of data derived from national sources and included wages/salary, salary on-costs, capital and other overheads, qualification costs, and the cost of monthly supervision where relevant. In estimating the unit cost of each type of therapist per hour of client contact, the ratio of direct (face-to-face) to indirect time (reflecting time for preparation of therapeutic sessions and other administrative tasks) of the therapist was also taken into account. This ratio of direct to indirect time was either directly obtained, where available, from national sources (Curtis 2020) or estimated by the committee, using their expertise and after taking into account relevant information in the same document.

Unit cost elements associated with wages/salary, salary on-costs, capital and other overheads were obtained, for each salary band level, from national data for community-based health care scientific and professional staff (Curtis 2020).

Qualification costs were estimated from a variety of sources. The qualification cost of a PWP was assumed to equal a 1-year cost of a AfC Band 4 health professional, which is the salary of PWP trainees (https://www.healthcareers.nhs.uk/explore-roles/psychological-therapies/roles/psychological-wellbeing-practitioner). The qualification cost of a band 7 high intensity therapist is variant, ranging from the qualification cost of a therapist originally trained as PWP to the qualification cost of a clinical psychologist (NHS England and Health Education England 2016b). Other high intensity therapists (counsellors, nurses) have qualification costs that lie between the PWP and the clinical psychologist qualification cost. For simplicity, the mean qualification cost of a band 7 high intensity therapist was calculated as the average between the PWP and the clinical psychologist qualification cost. In addition, for all band 7 high intensity therapists, regardless of their background qualifications, an additional IAPT high intensity therapist training cost of £10,000 (committee's expert advice) was estimated. The qualification cost of a band 6 therapist was estimated as the average between the PWP qualification cost (plus the £10,000 IAPT training cost) and a clinical psychology year 2 trainee cost (NHS England and Health Education England 2016b). Delivery of MBCT by high intensity therapists requires extra training that is not included in qualification costs. This training cost was estimated to approximate on average £18,000 per trainee, based on published fees for MBCT training courses offered by the Universities of Oxford and Bangor. All qualification costs were uplifted, where needed, to 2020 prices using the NHS cost inflation index (Curtis 2020) and annuitised using the formula reported in Netten 1998, assuming a useful working life ranging between 23-25 years, a time from obtaining the qualification until retirement ranging between 41-44 years, and an equal distribution of the useful working life over the period until retirement, due to lack of specific information on this distribution.

Other ongoing training costs of healthcare professionals delivering psychological interventions were not considered, because no relevant data are available. It is noted that this approach is consistent with the lack of consideration of ongoing training costs in the estimation of the reported GP unit cost, also due to lack of relevant data.

The committee also advised that supervision costs be considered in the estimation of the therapist unit costs, as supervision is essential for the delivery of psychological therapies and may incur considerable costs. According to the British Association for Behavioural and Cognitive Therapies (2016), high intensity therapists should receive regular supervision in groups of no more than 6 participants, with a mean duration of 1.5 hour per month for a full time practitioner. Based on this information, supplemented with the committee's expert advice, the supervision cost estimated for high intensity therapists comprised 1.5 hour of individual supervision per month, delivered by a Band 7 (50%) or Band 8a (50%) therapist. Low intensity therapists were assumed to receive 2 hours of individual supervision per month plus 2 hours of group supervision in groups of 4 by a band 6 PWP. The supervision cost included the cost of the supervisor's time, but not the cost of the supervised therapist's time, as this is indirectly included in the unit cost of each therapist.

Using the above information and assumptions, the unit costs of each therapist providing psychological interventions considered in the model are summarised in Table 87. Details on the methods of estimation of each unit cost are provided in Table 88, Table 89, and Table 90.

Table 87. Unit costs of therapists delivering psychological interventions used in the guideline economic analysis (2020 prices)

Type of therapist	Unit cost[1]	Details
PWP (Band 5)	£50	See Table 88
High intensity therapist Band 7	£110	See Table 89
High intensity MBCT therapist Band 7	£112	See Table 89
Therapist Band 6	£89	See Table 90
Therapist Band 6 with training in MBCT	£91	See Table 90

1 per hour of client contact
MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

Table 88. Unit cost of psychological well-being practitioner band 5 (2020 prices)

Cost element	Cost	Source
Wages – salary – annual	£25,023	Curtis 2020; costs for community-based scientific and professional staff AfC band 5
Salary on-costs – annual	£7,437	
Overheads, staff – annual	£7,953	
Overheads, non-staff – annual	£12,400	
Capital overheads – annual	£5,237	
Qualifications – annuitised	£4,141	Based on a 1-year cost of £50,659 for community-based scientific and professional staff AfC band 4 (salary level of PWP trainee) (Curtis 2020), annuitised using the formula by Netten 1998, assuming a useful working life of 25 years, a period life up to retirement of 44 years, and an equal distribution of the useful working life over the period until retirement.
Supervision – annual	£1,249	Assuming 2 hours of individual supervision per month plus 2 hours of group supervision in groups of 4, for a period of 42.6 weeks per year (working time per year), by a band 6 PWP (with unit cost per hour estimated using salary cost elements from Curtis 2020 plus annuitised qualification cost of £4,141).
SUM of unit costs	**£63,440**	
Working time (hours/year)	1,599	Curtis 2020
Total cost per hour	**£40**	

Cost element	Cost	Source
Ratio of direct to indirect time*	1-to-0.25	assumption - committee's expert opinion
Cost/hour of direct contact	**£50**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change

Table 89. Unit cost of high intensity therapist band 7 (with and without MBCT qualification) (2020 prices)

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Wages – salary – annual	£41,226		Curtis 2020; costs for community-based scientific and professional staff AfC band 7
Salary on-costs – annual	£13,024		
Overheads, staff – annual	£13,291		
Overheads, non-staff – annual	£20,723		
Capital overheads – annual	£5,237		
Qualifications – annuitised	£10,821	£12,485	Based on the average of the qualification cost of a therapist with a PWP background and that of a clinical psychologist. Former estimated from the trainee PWP cost (AfC band 4 salary for 1 year) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. Latter estimated from 3-year training cost of clinical psychologist (NHS England and Health Education England 2016b) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 23 years, a time up to retirement of 42 years, and equal distribution of useful working life over the period until retirement. For MBCT therapists, a 2-year MBCT training cost of £18,000 was added, obtained as an average of fees of respective courses offered by universities of Oxford and Bangor, annuitised using the formula by Netten 1998, assuming a useful working life of 22 years, a time up to retirement of 41 years, and equal distribution of useful working life over the period until retirement.
Supervision – annual	£1,037	£1,053	Assuming 1.5 hour of individual supervision per month, for a period of 42.6 weeks (working time per year), delivered by a Band 7 (50%) or Band 8a (50%) therapist (unit costs per hour estimated using salary cost elements from Curtis 2020 and qualification costs for therapists with/without MBCT training).
SUM of unit costs	**£105,359**	**£107,038**	
Working time (hours/year)	1599		Curtis 2020
Total cost per hour	**£66**	**£67**	

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Ratio of direct to indirect time*	60-to-40		Based on the committee's expert opinion and a review of respective ratios for health professionals delivering psychological therapies (Curtis 2020)
Cost/hour of direct contact	**£110**	**£112**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change; MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

Table 90. Unit cost of therapist band 6 (with/without MBCT qualification) (2020 prices)

Cost element	Cost		Source
	without MBCT training	with MBCT training	
Wages – salary – annual	£33,734		Curtis 2020; costs for community-based scientific and professional staff AfC band 6
Salary on-costs – annual	£10,440		
Overheads, staff – annual	£10,823		
Overheads, non-staff – annual	£16,875		
Capital overheads – annual	£5,237		
Qualifications – annuitised	£7,527	£9,190	Based on the average of the qualification cost of a therapist with a PWP background and that of a clinical psychologist trainee in year 2. Former estimated from the trainee PWP cost (AfC band 4 salary for 1 year) plus the IAPT training cost (£10,000), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. Latter estimated from training cost of clinical psychologist up to 2 years of training (NHS England and Health Education England 2016b), annuitised using the formula by Netten 1998, assuming a useful working life of 24 years, a time up to retirement of 43 years, and equal distribution of useful working life over the period until retirement. For MBCT therapists, a 2-year MBCT training cost of £18,000 was added, obtained as an average of fees of respective courses offered by universities of Oxford and Bangor, annuitised using the formula by Netten 1998, assuming a useful working life of 22 years, a time up to retirement of 41 years, and equal distribution of useful working life over the period until retirement.
Supervision – annual	£1,037	£1,053	Assuming 1.5 hour of individual supervision per month, for a period of 42.6 weeks (working time per year), delivered by a Band 7 (50%) or Band 8a (50%) therapist (unit costs per hour estimated using salary cost elements from

Cost element	Cost		Source
	without MBCT training	with MBCT training	
			Curtis 2020 and qualification costs for band 7 and 8 therapists with/without MBCT training).
SUM of unit costs	**£85,673**	**£87,352**	
Working time (hours/year)	1599		Curtis 2020
Total cost per hour	**£54**	**£55**	
Ratio of direct to indirect time*	60-to-40		Based on the committee's expert opinion and a review of respective ratios for health professionals delivering psychological therapies (Curtis 2020)
Cost/hour of direct contact	**£89**	**£91**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change; MBCT: mindfulness-based cognitive therapy; PWP: psychological well-being practitioner

In addition to therapists' time, the intervention costs of all psychological therapies included an initial GP visit for referral to psychological services. It is acknowledged that this assumption (100% GP referral to psychological services) is a conservative estimate, as a proportion of people with a new episode of depression may self-refer to psychological services. On the other hand, it is possible that some of the people self-referring may have consulted their GP prior to self-referral. The impact of this assumption was tested in a sensitivity analysis, under a scenario that assumed 100% self-referral to psychological services.

Moreover, the intervention costs of computerised self-help therapies included the cost of the provider of digital mental health programmes and related equipment required for their delivery (personal computers [PCs] and capital overheads). The cost of provision of a computerised CBT programme per client by the main provider of digital mental health programmes comprised a fixed fee of £39, which is independent of the number of sessions attended (committee's expert advice). The annual costs of hardware and capital overheads (space around the PC) were based on reported estimates made for the economic analysis undertaken to inform the NICE Technology Appraisal on computerised CBT for depression and anxiety (Kaltenthaler 2006). Kaltenthaler 2006 estimated that one PC can serve around 100 people with mental disorders treated with computerised programmes per year. Assuming that a PC is used under full capacity (that is, it serves no less than 100 people annually, considering that it is available for use not only by people with depression, but also by people with other mental health conditions), the annual cost of hardware and capital overheads was divided by 100 users, leading to a hardware and capital overheads cost per user of £14 (2020 price). It must be noted that if users of such programmes can access them from home or a public library, then the cost of hardware and capital overheads to the NHS is zero.

Details on the resource use and total costs of psychological interventions for less and more severe depression are provided in Table 91.

Table 91. Intervention costs of psychological therapies for adults with a new episode of depression considered in the guideline economic analysis (2020 prices)

Intervention	Resource use details	Total intervention cost per person[1]
Computerised CBT without support – LS and MS depression	Fixed cost of provider of digital mental health programmes is £39 per person (committee information); cost of hardware & capital overheads £14 per person (2020 price, based on Kaltenthaler 2006). Cost includes 30 minutes of setup time by a band 5 PWP.	£78 + £39
Computerised CBT with support – LS and MS depression	1 session of 30 minutes and 7 sessions of 15 minutes each = 2.25 therapist hours per service user (band 5 PWP); fixed cost of provider of digital mental health programmes £39 per person (committee information); cost of hardware & capital overheads £14 per person (2020 price, based on Kaltenthaler 2006)	£165 + £39
BA individual – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
BA group – LS depression	8 sessions x 90 minutes each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 24 therapist hours per group and 3 therapist hours per service user	£297 + £39
CBT individual < 15 sessions – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
CBT group < 15 sessions – LS depression	8 sessions x 90 minutes each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 24 therapist hours per group and 3 therapist hours per service user	£297 + £39
Problem solving individual – LS depression	1 session of 60 minutes and 5 sessions of 30 minutes = 3.5 therapist hours per service user (band 5 PWP)	£174 + £39
Non-directive counselling individual – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
IPT individual – LS depression	8 sessions x 1 hour each = 8 therapist hours per service user (band 7 HI therapist)	£873 + £39
Short term PDPT individual – LS depression	12 sessions x 1 hour each = 12 therapist hours per service user (band 7 HI therapist)	£1,310 + £39
MBCT group – LS depression	8 sessions x 2 hours each; 2 MBCT therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 32 therapist hours per group and 4 therapist hours per service user	£405 + £39
BA individual – MS depression	12 sessions x 1 hour each = 12 therapist hours per service user (band 7 HI therapist)	£1,310 + £39
CBT individual ≥ 15 sessions – MS depression	16 sessions x 1 hour each = 16 therapist hours per service user (band 7 HI therapist)	£1,746 + £39
CBT group < 15 sessions – MS depression	10 sessions x 1.5 hours each; 2 therapists (1 band 7 HI and 1 band 6) and 8 participants per group = 30 therapist hours per group and 3.75 therapist hours per service user	£372 + £39
Problem solving individual – MS depression	1 session of 60 minutes and 8 sessions of 30 minutes = 5 therapist hours per service user (band 5 PWP)	£248 + £39

Intervention	Resource use details	Total intervention cost per person[1]
Non-directive counselling individual – MS depression	12 sessions x 1 hour each = 12 therapist hours per service user (band 7 HI therapist)	£1,310 + £39
IPT individual – MS depression	16 sessions x 1 hour each = 16 therapist hours per service user (band 7 HI therapist)	£1,746 + £39
Short term PDPT individual – MS depression	16 sessions x 1 hour each = 16 therapist hours per service user (band 7 HI therapist)	£1,746 + £39

[1] Cost of psychological intervention plus 1 GP referral visit, at a GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020); cost of psychological intervention based on resource use combined with unit cost of the appropriate level of therapist, estimated as described in Table 88, Table 89 and Table 90.
BA: behavioural activation; CBT: cognitive behavioural therapy; HI: high intensity; IPT: interpersonal psychotherapy; LS: less severe; MS: more severe; PDPT: psychodynamic psychotherapy; PWP: psychological well-being practitioner

Physical interventions

Resource use estimates for supervised high intensity exercise (individual and group) and for acupuncture were estimated based on resource use data described in respective RCTs that were included in the guideline NMA that informed the economic analysis (see Appendix N), modified by the committee to represent routinely offered exercise programmes in the UK. It is acknowledged that exercise programmes are not routinely offered within the NHS context, although people with depression may be advised to attend exercise programmes at their own expense. Nevertheless, in order to consider the potential cost of such interventions to the NHS, exercise programmes were assumed to be delivered by an AfC band 5 practitioner, with a unit cost equivalent to that of PWP (although it is acknowledged that a different professional group, and not a PWP, may deliver this intervention within the NHS). Acupuncture is also not routinely offered for the management of depression within the NHS setting. In order to consider the potential cost of acupuncture to the NHS, it was assumed that this is delivered by AfC band 6 physiotherapists, which is the salary band level at which a practitioner can carry out invasive interventions. For acupuncture, an additional £1 cost per session was included for consumables (disposable needles).

The PWP unit cost was estimated at £50 per hour of client contact as shown in Table 88. The cost of band 6 physiotherapist was estimated at £71 per hour of client contact as shown in Table 92.

Table 92. Unit cost of physiotherapist band 6 (2020 prices)

Cost element	Cost	Source
Wages – salary – annual	£33,734	Curtis 2020; costs for community-based scientific and professional staff AfC band 6
Salary on-costs – annual	£10,440	
Overheads, staff – annual	£10,823	
Overheads, non-staff – annual	£16,875	
Capital overheads – annual	£5,237	
Qualifications – annuitised	£5,446	
SUM of unit costs	**£82,555**	
Working time (hours/year)	£1,599	
Total cost per hour	**£52**	
Ratio of direct to indirect time*	1-to-0.37	
Cost/hour of direct contact	**£71**	

** Ratio of face-to-face time to time for preparation and other administrative tasks*
AfC: agenda for change

In addition, the intervention costs of all physical treatments included an initial GP visit for referral to each service.

Details on the resource use and total costs of physical interventions for less and more severe depression are provided in Table 93.

Table 93. Intervention cost of physical interventions for adults with a new episode of depression considered in the guideline economic analysis (2020 prices)

Intervention	Resource use details	Total intervention cost per person[1]
Exercise individual – LS depression	25 sessions x 1 hour each = 25 therapist hours per service user (unit cost equivalent to band 5 PWP)	£1,240 + £39
Exercise group – LS depression	30 sessions x 1 hour each; 1 therapist (unit cost equivalent to band 5 PWP) and 8 participants per	£186 + £39

Intervention	Resource use details	Total intervention cost per person[1]
	group = 30 therapist hours per group and 3.75 therapist hours per service user	
Exercise individual – MS depression	30 sessions x 1 hour each = 30 therapist hours per service user (unit cost equivalent to band 5 PWP)	£1,488 + £39
Exercise group – MS depression	40 sessions x 1 hour each; 1 therapist (unit cost equivalent to band 5 PWP) and 8 participants per group = 40 therapist hours per group and 5 therapist hours per service user	£248 + £39
Acupuncture – MS depression	25 sessions x 30 minutes each = 12.5 acupuncturist hours per service user (band 6 physiotherapist) plus cost of needles of £1 per session (assumption)	£909 + £39

[1] Cost of physical interventions plus 1 GP visit, at a GP unit cost £39 per patient contact lasting 9.22 minutes (Curtis 2020); cost of physical interventions based on resource use combined, as relevant, with the unit cost of a band 5 PWP, estimated at £42 per hour of direct client contact as described in Table 88, or the unit cost of a band 6 physiotherapist, as described in Table 92.
LS: less severe; MS: more severe; PWP: psychological well-being practitioner

Combined pharmacological and psychological interventions

The intervention cost of combined interventions was estimated as the sum of the intervention costs of the individual treatment components.

In cohorts receiving a pharmacological intervention combined with a psychological or physical intervention, no extra GP visits were added in the psychological or physical intervention, since people were already receiving GP care as part of their antidepressant treatment.

Intervention costs in people who discontinued treatment early

People who discontinued treatment early consumed part of the acute intervention resources: people who discontinued pharmacological treatment incurred the cost of 1 GP visit and 1 pack of drugs (and lab testing at initiation of treatment, where relevant); people who discontinued a high intensity individual psychological therapy incurred the cost of 25% of the intended number of visits plus the initial GP visit; people who discontinued computerised CBT incurred the cost of the initial GP visit, the full fixed cost of the provider of the programme plus the cost of 2 of the therapist contacts if they attended a therapist supported programme. People under GP care who discontinued treatment incurred the cost of 1 GP visit. People who discontinued a group psychological therapy or group exercise were assumed to incur the full cost of therapy, since participants in a group intervention are not replaced in the group if they discontinue and therefore the full cost of therapy per participant is incurred, whether the participant attends the full course or not.

Interventions received as continuation treatments aiming at preventing relapses

People with more severe depression that responded to treatment moved on to an appropriate relapse preventive intervention, the cost of which was based on the resource use estimates made to inform the guideline economic modelling of interventions for relapse prevention that is described in Evidence review C, appendix J.

An overview of the resource use and cost estimates of relapse preventive interventions received by the cohorts who responded to treatment of a new depressive episode is shown in Table 94.

Table 94. Intervention costs of continuation treatments considered in the guideline economic analysis on relapse prevention (2020 prices)

Maintenance treatment	Resource use	Total cost
Sertraline **Escitalopram** **Lofepramine** **Duloxetine** **Mirtazapine** **Trazodone**	Same dosage as in acute treatment with drug tapering represented as a linear reduction in dosage over the 3 last months of maintenance treatment (which lasted 2 years in total) plus 6 GP visits in the 1st year and 3 GP visits in the 2nd year, plus 3 GP visits during tapering	£552 £503 £924 £567 £512 £538
GP care & AD drug tapering	3 GP visits in the first year plus 1 extra GP visit for drug tapering plus linear reduction of the drug dosage over a month; 1 GP visit in the second year	£196-£205 depending on drug
4 sessions of individual psychological therapy	4 individual sessions lasting 1 hour each = 4 therapist hours per service user (HI therapist Band 7), plus 2 GP visits	£517 + £78
MBCT	8 group sessions + 4 group booster sessions lasting 2 hours each; 2 MBCT therapists (1 HI Band 7 and 1 Band 6) and 8 participants per group, plus 2 GP visits	£608 + £78
Group CBT	8 group sessions lasting 2 hours each; 2 therapists (1 HI Band 7 and 1 Band 6) and 8 participants per group, plus 2 GP visits	£398 + £78
GP care	3 GP visits in the first year and 1 GP visit in the second year	£156

Unit costs of drugs and health professionals shown in Table 86 and Table 87, respectively.
AD: antidepressant; CBT: cognitive behavioural therapy; HI: high intensity; MBCT: mindfulness-based cognitive therapy

Other healthcare costs considered in the economic analysis

Healthcare costs associated with the Markov states of remission and depressive episode

The costs of the states of remission and depressive episode in the Markov component of the economic model were estimated using primarily data from Byford 2011. This was a naturalistic, longitudinal study that aimed to estimate the health service use and costs associated with non-remission in people with depression using data from a large primary care UK general practice research database between 2001 and 2006. The study analysed 12-month healthcare resource use data on 88,935 adults with depression and in receipt of at least two antidepressant prescriptions (for amitriptyline, citalopram, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) in the first 3 months after the index prescription. The study provided data on resource relating to medication (antidepressant use and concomitant medication such as anxiolytics, hypnotics, mood stabilizers and neuroleptics), GP contacts, psychological therapy, psychiatrist and other specialist contacts, inpatient stays and accident and emergency attendances. Data were reported separately for people who remitted within 12 months, and those who did not remit.

The study provided cost data for the subgroup of study participants with severe depression. Using the cost figures reported in the paper and the numbers of people in each remission status and symptom severity level it was possible to estimate costs for adults with non-severe (mild or moderate) depression. The cost figures corresponding to each remission status and level of symptom severity are shown in Table 95.

Table 95. Healthcare costs of adults with depression who remitted within 12 months and people who did not remit within 12 months from index prescription, by symptom severity status, as reported in Byford 2011

Remission status	Cost and N in each category		
	All levels of symptom severity N = 88,935 (reported costs)	Severe depression N = 8,106 (reported costs)	Mild or moderate depression N = 80,829 (estimated costs)
People who remitted within 12 months	£656 (N=53,654)	£749 (N=4,423)	£648 (N= 49,231)
People who did not remit within 12 months	£973 (N=35,281)	£1,037 (N=3,683)	£966 (N=31,598)

Costs for severe depression could be potentially attached to states experienced by adults with more severe depression in the economic model, while costs for mild or moderate depression could be potentially attached to states experienced by adults with less severe depression. However, it can be seen that the mean healthcare costs of people with mild or moderate depression were very similar (only 1% lower) to the respective mean healthcare costs of all participants in the study. Mean costs of people with severe depression were somewhat higher than the mean respective costs of the total study sample (7% higher for people who did not remit and 14% higher for people who remitted). These differences in costs according to symptom severity were not considered to have a substantial impact on the model results. Moreover, adults with severe depression in the study are likely to have more severe symptoms than adults with more severe depression in the economic analysis (which includes people with moderate and severe depression). Therefore, it was decided to use the mean total costs reported in the study for the whole study sample (regardless of symptom severity) as the basis for estimation of healthcare costs for people with both less severe and more severe depression. These costs were tested in sensitivity analysis.

Healthcare resource use and cost data reported for the whole study sample in Byford 2011 were modified following the committee's advice and attached to the health states of the Markov component of the economic model: data on people in a depressive episode who remitted within 12 months in the study were attached onto people in the depressive state of the model if they were expected to move to the remission state in the following year. Resource use and cost data on people who did not remit within 12 months in the naturalistic study were used as the basis for estimating healthcare costs incurred by people who were expected to remain in the depressive episode state in the next cycle of the model. Costs incurred after remission was achieved in the naturalistic study were used to estimate annual healthcare costs associated with the remission state of the model. In people that experienced remission whilst being in the Markov component of the model (i.e. not those entering the Markov component in the remission state), an annual cost of maintenance drug treatment plus the cost of 3 GP visits was added to this figure for the first year of remission only, to reflect optimal maintenance antidepressant therapy after remission was achieved, as discussed in Evidence review C, appendix J.

Following the committee's advice, some of the resource use and drug acquisition cost data reported in the paper were modified, to reflect current clinical practice and the fact that some drugs are now available off-patent. Where detailed resource use data were provided, these were combined with appropriate 2020 unit costs; where only cost figures were available, these have been uplifted to 2020 prices using the hospital & community health services (HCHS) index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020), so that all costs in the guideline economic analysis reflect 2020 prices.

Details on the methods used to modify and update the resource use and unit costs reported in Byford 2011 in order to estimate costs associated with the 2 states of the Markov model

component are provided in Evidence review C, appendix J. The healthcare costs associated with each health state in the Markov component of the guideline economic model of treatments for new episodes of depression are presented in Table 96.

Table 96. Annual healthcare costs associated with the states of remission and depressive episode in the guideline economic analysis (2020 prices)

Health state	Cost	Comments
Depressive episode – people expected to remain in this state in the next model cycle	£1,449	Includes costs of antidepressants, concomitant medication, GP visits or phone calls, psychological therapy contacts, psychiatrist or other specialist contacts, hospitalisations, and accident and emergency attendances. Costs estimated by multiplying relevant resource use for non-remitters and remitters reported in Byford 2011 with appropriate national unit costs for 2020 (Curtis 2020). Treatment costs estimated by published sources of relevant resource use and costs Radhakrishnan 2013; NHS England 2016. All costs expressed in 2020 prices using the hospital & community health services inflation index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020) and the estimated net ingredient cost per antidepressant or concomitant medication prescription item ratio for 2015:2006, estimated using national data (NHS The Information Centre 2007; NHS Business Services Authority 2020 (Details provided in Evidence review C, table 110)
Depressive episode – people expected to move to the remission state in the next model cycle	£1,102	
Remission	£528	3-month healthcare cost of people having achieved remission obtained from graphs published by Byford 2011, read using digital software (http://www.digitizeit.de), extrapolated to 12 months and uplifted to 2020 prices using the HCHS inflation index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020).
Maintenance antidepressant therapy – 1st year extra cost	£136	Additional cost reflecting optimal duration of maintenance antidepressant therapy following remission, comprising an annual antidepressant drug cost equal to that estimated for remitters and 3 GP contacts at the GP unit cost of £39 per patient contact lasting 9.22 minutes for 2020 (Curtis 2020). This was considered only in people experiencing a remission while being in the Markov model, not in those entering the Markov model in the remission state; the latter received an active relapse preventive intervention or no relapse preventive intervention.

Treatment costs in people who discontinued initiated treatment early in the decision-tree component of the model

People who switched to a mixture of available treatments following early treatment discontinuation were assumed to incur a 'mixed treatment' cost over 8 out of the 12 weeks of the decision-tree. This cost was estimated as a proportion (8/52) of the annual cost of a depressive episode (for people remaining in depression for longer than one model cycle) that was estimated for the Markov component of the model, which equalled £223.

The cost of no treatment over 8 weeks was assumed to be zero; over this period people receiving no treatment were assumed to incur no depression-specific costs. However, those who entered the depressive state of the Markov model were assumed to re-start receiving depression-related care and incur the cost associated with the depressive Markov state.

Cost of management of intolerable and tolerable common side effects from antidepressant treatment

People who discontinued antidepressant or combined treatment due to intolerable side effects were assumed to have one extra GP contact costing £39 (Curtis 2020).

People who experienced common side effects were assumed to have one extra GP contact every 3 months costing £39 (Curtis 2020) and to consume a cost of £10 per year for medication relating to the management of common side effects (for example, paracetamol or anti-inflammatory drugs for headaches).

Discounting

Costs and benefits were discounted at an annual rate of 3.5% in the second year of the Markov component of the model as recommended by NICE 2014.

Handling uncertainty

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probabilistic distributions (rather than being expressed as point estimates); this approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each intervention) were calculated by averaging across the 10,000 iterations. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs 2006).

The distributions of the odds ratios of relative effects of all treatments versus the reference treatment were obtained from the respective NMAs, defined directly from values recorded in each of the 10,000 iterations performed in OpenBUGS.

Beta distribution was assigned to the following parameters: proportion of women in the study sample; the baseline risks of discontinuation and discontinuation due to side effects in those discontinuing; the proportion of people experiencing side effects; the probability of responders with more severe depression who moved to the remission state of the Markov model; and the probability of moving to specific relapse preventive treatments following successful completion of acute treatment (in adults with more severe depression). Utility values were also assigned a beta distribution after applying the method of moments on data reported in the relevant literature.

The 12-month probabilities of response and remission at various levels of symptom severity were given a beta distribution. The probabilities of response and remission following acute treatment, as well as the probability of remission and the baseline risk of relapse after a single (first) episode that were utilised in the Markov component of the model were determined by a Weibull distribution, as described earlier. The probability distributions of the Weibull parameters (gamma and lambda) of recovery (‘baseline recovery’) that came from evidence synthesis in OpenBUGS were defined directly from values recorded in each of 10,000 iterations performed in OpenBUGS. This allowed the correlation between the Weibull parameters to be taken into account. The 12-month probabilities of response and remission at various levels of symptom severity and the 12-month probability of ‘baseline recovery’ estimated from data synthesis were used to estimate hazard ratios of each parameter versus baseline recovery (see Table 79). These hazard ratios were then applied onto the ‘baseline’ lambda value obtained from data synthesis, in order to maintain the correlation between the lambda parameters for response and remission at each severity level and the gamma parameter that was estimated from data synthesis.

The hazard ratio of the risk of relapse for every additional depressive episode that was utilised in the Markov element of the model was given a log-normal distribution. The risk ratio of mortality was also assigned a log-normal distribution.

Uncertainty in intervention costs was taken into account by assigning probability distributions to the number of GP contacts and the number of individually delivered psychological therapy sessions. Different distributions around the number of GP contacts were used for people receiving active pharmacological interventions and for those receiving only GP care (reference treatment). The number of therapist sessions per person attending group psychological interventions was not assigned a probability distribution because the number of group sessions remains the same, whether a participant attends the full course of treatment or a lower number of sessions. Drug acquisition costs were not given a probability distribution as these costs are set and characterised by minimal uncertainty. However, if people receiving maintenance pharmacological therapy attended fewer GP visits than the mode in the second year of maintenance treatment, then they were assumed to be prescribed smaller amounts of medication than optimal, and to subsequently incur lower drug acquisition costs. Unit costs of healthcare staff (GPs and therapists delivering psychological and physical interventions) were assigned a normal distribution.

Healthcare costs associated with discontinuation of acute treatment and the states of relapse and remission in the Markov element of the model were assigned a gamma distribution.

Table 97 reports the mean values of all input parameters utilised in the economic model and provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

A number of deterministic one-way sensitivity analyses were undertaken to explore the impact of alternative hypotheses on the results. The following scenarios were explored:

- Change in the number of previous episodes, resulting in a change in the risk of relapse in the Markov component of the model; the number of previous episodes was increased from 0 to 2 in adults with less severe depression and was varied between 0 and 5 in adults with more severe depression
- Use of higher utility values of 0.65 and 0.56 for less severe and more severe depression, respectively, reported in Mann 2009
- Use of the value of 0.70 for remission reported in Kolovos 2017; and 0.62 for response not reaching remission reported in Koeser 2015.
- Changing the cost of a depressive episode (relapse) by ±50%
- Change in the baseline discontinuation of SSRIs by ± 20%.
- Use of a probability of developing side effects of 0.40 throughout the period people under pharmacological antidepressant treatment received antidepressants.
- Assuming that 100% of people attending psychological services have self-referred (instead of being referred to services by their GP)
- Assuming the same number of sessions across all individual high intensity psychological interventions, either a lower number of sessions (8 sessions for less severe depression and 12 sessions for more severe depression) or a higher number of sessions (12 sessions for less severe depression and 16 sessions for more severe depression). At the same time, the number of group psychological interventions was doubled, to explore the impact of change in resource use intensity on the relative cost effectiveness between group and individual psychological interventions.

In addition, a probabilistic bias-adjusted economic analysis was conducted for adults with more severe depression, using bias-adjusted data on discontinuation for any reason and response in completers, derived from the bias-adjusted NMA models, as described earlier.

The bias-adjusted data for adults with more severe depression that were used in the probabilistic sensitivity analysis are also shown in Table 97.

Table 97. Input parameters (deterministic values and probability distributions) that informed the economic models of interventions for the treatment of a new depressive episode in adults with less severe depression and adults with more severe depression

Input parameter	Deterministic value	Probability distribution	Source of data - comments
General characteristics of population			
Age of onset (years)	32	No distribution	Kessler 2005; Fernandez 2015; committee's advice
Mean interval between episodes (years)	2	No distribution	Committee's expert opinion
Number of previous episodes			
- less severe depression	0	No distribution	Committee's expert advice
- more severe depression	2	No distribution	
Proportion of women	0.56	Beta: α=279; β=219	McManus 2016; weighted prevalence of depression 2.9% in men, 3.7% in women, survey sample N=7,546
Adults with less severe depression: discontinuation – log-odds ratios vs sertraline			
Loferpamine	0.21	-1.32 to 1.78	Guideline NMA; distribution based on 10,000 iterations
cCBT without or with minimal support	-0.64	-5.55 to 2.92	
cCBT with support	-0.65	-5.61 to 2.94	
Individual BA	-1.80	-7.09 to 2.55	
Group BA	-0.33	-5.26 to 3.33	
Individual CBT (<15 sessions)	-1.42	-6.30 to 2.17	
Group CBT (<15 sessions)	-0.94	-5.95 to 2.81	
Individual problem solving	-0.50	-5.41 to 3.15	
Non-directive counselling	-1.80	-6.86 to 2.01	
Individual IPT	-0.56	-5.63 to 2.79	
Individual short-term PDPT	-2.12	-7.17 to 1.75	
Group MBCT	-0.83	-5.76 to 2.82	
Supervised HI individual exercise	-1.43	-6.54 to 2.35	
Supervised HI group exercise	-0.86	-5.89 to 2.87	
GP care [TAU]	-0.81	-5.77 to 2.70	
Adults with less severe depression: discontinuation due to side effects in those discontinuing treatment – log-odds ratios vs SSRIs			
TCAs (lofepramine)	3.32	-0.22 to 6.88	Guideline NMA; distribution based on 10,000 iterations

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Adults with less severe depression: response in completers – log-odds ratios vs GP care (TAU)			
Sertraline	2.01	0.03 to 3.98	Guideline NMA; distribution based on 10,000 iterations
Loferpamine	3.15	0.04 to 6.23	
cCBT without or with minimal support	0.85	-0.47 to 2.15	
cCBT with support (class effect)	0.95	-1.03 to 2.86	
Individual BA	1.83	-0.29 to 3.93	
Group BA	3.02	1.05 to 5.02	
Individual CBT (<15 sessions)	1.79	0.15 to 3.43	
Group CBT (<15 sessions)	4.63	2.44 to 6.87	
Individual problem solving	0.26	-1.14 to 1.66	
Non-directive counselling	1.16	-2.55 to 4.79	
Individual IPT	1.04	-0.28 to 2.36	
Individual short-term PDPT	1.63	-1.18 to 4.45	
Group MBCT	1.72	0.00 to 3.40	
Supervised HI individual exercise	1.16	-0.47 to 2.79	
Supervised HI group exercise	1.43	-0.12 to 2.95	
No treatment	-0.16	-1.43 to 1.10	
Adults with more severe depression: discontinuation, base-case analysis – log-odds ratios vs escitalopram			
Lofepramine	0.10	-0.18 to 0.33	Guideline NMA; distribution based on 10,000 iterations; data for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥ 15sessions) + imipramine; data for traditional acupuncture + escitalopram borrowed from traditional acupuncture + paroxetine
Duloxetine	0.14	-0.02 to 0.33	
Mirtazapine	0.06	-0.14 to 0.26	
Trazodone	0.35	0.10 to 0.60	
cCBT without or with minimal support	-0.22	-1.08 to 0.67	
cCBT with support	-0.19	-0.90 to 0.51	
Individual BA	-0.65	-1.33 to 0.03	
Individual CBT (≥15 sessions)	-0.43	-0.88 to 0.01	
Group CBT (<15 sessions)	-0.31	-1.32 to 0.68	
Individual problem solving	-0.64	-1.47 to 0.16	
Non-directive counselling	-0.35	-1.15 to 0.45	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Individual IPT	-0.68	-1.51 to 0.15	
Individual short-term PDPT	0.04	-0.85 to 0.95	
Supervised HI individual exercise	0.14	-0.88 to 1.23	
Supervised HI group exercise	0.26	-0.42 to 0.93	
Traditional acupuncture	-0.25	-1.28 to 0.64	
Individual CBT (≥ 15sessions) + escitalopram	-0.32	-1.22 to 0.51	
Traditional acupuncture + escitalopram	-0.27	-1.51 to 0.96	
GP care [placebo]	0.13	0.02 to 0.24	
Adults with more severe depression: discontinuation, bias-adjusted analysis – log-odds ratios vs escitalopram			
Lofepramine	0.11	-0.16 to 0.34	Guideline NMA; distribution based on 10,000 iterations; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥ 15sessions) + imipramine; effect for traditional acupuncture + escitalopram borrowed from traditional acupuncture + paroxetine
Duloxetine	0.14	-0.01 to 0.33	
Mirtazapine	0.07	-0.13 to 0.26	
Trazodone	0.34	0.08 to 0.59	
cCBT without or with minimal support	-0.19	-1.10 to 0.73	
cCBT with support	-0.16	-0.91 to 0.58	
Individual BA	-0.68	-1.39 to 0.02	
Individual CBT (≥15 sessions)	-0.36	-0.82 to 0.10	
Group CBT (<15 sessions)	-0.21	-1.30 to 0.88	
Individual problem solving	-0.71	-1.62 to 0.18	
Non-directive counselling	-0.33	-1.15 to 0.51	
Individual IPT	-0.64	-1.49 to 0.18	
Individual short-term PDPT	0.11	-0.84 to 1.08	
Supervised HI individual exercise	0.21	-0.82 to 1.30	
Supervised HI group exercise	0.30	-0.41 to 1.01	
Traditional acupuncture	-0.37	-1.36 to 0.57	
Individual CBT (≥ 15sessions) + escitalopram	-0.28	-1.19 to 0.59	
Traditional acupuncture + escitalopram	-0.14	-1.39 to 1.10	
GP care [placebo]	0.08	-0.03 to 0.21	
Adults with more severe depression: discontinuation due to side effects in those discontinuing treatment – log-odds ratios vs SSRIs			

Input parameter	Deterministic value	Probability distribution	Source of data - comments
TCAs (lofepramine)	0.69	0.18 to 1.21	Guideline NMA; distribution based on 10,000 iterations; risk for individual CBT (≥ 15sessions) + escitalopram and for traditional acupuncture + escitalopram assumed to equal that for escitalopram alone
SNRIs (duloxetine)	0.40	-0.07 to 0.86	
Mirtazapine	0.03	-0.37 to 0.43	
Trazodone	0.26	-0.24 to 0.77	
Adults with more severe depression: response in completers, base-case analysis – log-odds ratios vs GP care (pill placebo)			
Escitalopram	0.81	0.60 to 1.00	Guideline NMA; distribution based on 10,000 iterations; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥15 sessions) + any SSRI; effect for traditional acupuncture + escitalopram borrowed from traditional acupuncture + any SSRI
Lofepramine	1.14	0.81 to 1.46	
Duloxetine	0.99	0.75 to 1.23	
Mirtazapine	1.02	0.70 to 1.33	
Trazodone	0.68	0.28 to 1.09	
cCBT without or with minimal support	0.12	-1.79 to 1.89	
cCBT with support	0.82	-0.36 to 2.02	
Individual BA	1.42	0.09 to 2.77	
Individual CBT (≥15 sessions)	1.22	0.55 to 1.89	
Group CBT (<15 sessions)	0.99	-0.27 to 2.21	
Individual problem solving	2.16	0.78 to 3.55	
Non-directive counselling	1.50	0.08 to 2.92	
Individual IPT	0.72	-0.31 to 1.73	
Individual short-term PDPT	1.58	-0.94 to 4.06	
Supervised HI individual exercise	2.40	-0.31 to 5.05	
Supervised HI group exercise	2.02	0.17 to 4.08	
Traditional acupuncture	-0.17	-1.38 to 1.01	
Individual CBT (≥ 15sessions) + escitalopram	1.84	0.61 to 3.00	
Traditional acupuncture + escitalopram	4.07	2.97 to 5.17	
No treatment	-0.27	-1.40 to 0.86	
Adults with more severe depression: response in completers, bias-adjusted analysis – log-odds ratios vs GP care (pill placebo)			
Escitalopram	0.65	0.43 to 0.85	Guideline NMA; distribution based on 10,000 iterations; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥15 sessions) + any SSRI; effect for
Lofepramine	0.87	0.53 to 1.20	
Duloxetine	0.84	0.59 to 1.08	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Mirtazapine	0.77	0.44 to 1.10	traditional acupuncture + escitalopram borrowed from traditional acupuncture + any SSRI
Trazodone	0.50	0.10 to 0.91	
cCBT without or with minimal support	-0.20	-2.26 to 1.67	
cCBT with support	0.39	-0.87 to 1.68	
Individual BA	1.18	-0.19 to 2.49	
Individual CBT (≥15 sessions)	0.92	0.21 to 1.62	
Group CBT (<15 sessions)	0.51	-0.76 to 1.81	
Individual problem solving	2.03	0.61 to 3.46	
Non-directive counselling	1.38	-0.06 to 2.83	
Individual IPT	0.43	-0.65 to 1.50	
Individual short-term PDPT	1.31	-1.21 to 3.81	
Supervised HI individual exercise	1.47	-1.69 to 4.73	
Supervised HI group exercise	1.63	-0.34 to 3.78	
Traditional acupuncture	-0.26	-1.49 to 0.93	
Individual CBT (≥ 15sessions) + escitalopram	1.68	0.43 to 2.82	
Traditional acupuncture + escitalopram	3.85	2.74 to 4.95	
No treatment	-0.24	-1.40 to 0.94	
Adults with more severe depression: remission in completers – log-odds ratios vs GP care (pill placebo)			
Escitalopram	0.56	0.44 to 0.71	Guideline NMA; distribution based on 10,000 iterations; effect for cCBT without or with minimal support borrowed from class effect; effect for individual CBT (≥ 15sessions) + escitalopram borrowed from individual CBT (≥15 sessions) + imipramine; effect for traditional acupuncture + escitalopram borrowed from traditional acupuncture + paroxetine
Lofepramine	0.70	-0.12 to 1.24	
Duloxetine	0.75	0.62 to 0.88	
Mirtazapine	0.61	0.34 to 0.89	
Trazodone	0.53	0.26 to 0.81	
cCBT without or with minimal support	1.38	-0.55 to 3.61	
cCBT with support	0.95	0.14 to 1.75	
Individual BA	1.08	0.45 to 1.71	
Individual CBT (≥15 sessions)	1.09	0.61 to 1.56	
Group CBT (<15 sessions)	0.29	-0.84 to 1.37	
Individual problem solving	1.15	0.19 to 2.14	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
Non-directive counselling Individual IPT Individual short-term PDPT Supervised HI individual exercise Supervised HI group exercise Traditional acupuncture Individual CBT (≥ 15sessions) + escitalopram Traditional acupuncture + escitalopram No treatment	0.30 1.00 0.50 0.32 0.63 0.10 1.72 0.46 0.17	-0.85 to 1.47 0.34 to 1.67 -0.47 to 1.45 -0.47 to 1.20 0.02 to 1.27 -1.58 to 1.80 0.81 to 2.91 -0.54 to 1.47 -0.52 to 0.87	
Baseline risk of discontinuation			
Less severe depression - sertraline More severe depression - escitalopram	0.38 0.34	Beta: α=191; β=309 Beta: α=169; β=331	Risk of discontinuation for SSRIs based on a review of studies (Bull 2002, Hansen 2004, Lewis 2004, Olfson 2006, Goethe 2007, Burton 2012) and further expert opinion. Risk of individual SSRI drugs estimated using the guideline NMA SSRI class and individual drug effects versus placebo. Distribution based on assumption.
Baseline risk of discontinuation due to side effects in those discontinuing			
Less severe depression - sertraline More severe depression - escitalopram	0.39 0.44	Beta: α=196; β=304 Beta: α=222; β=278	Based on discontinuation due to side effects data reported in Goethe 2007 and Bull 2002 for SSRIs, using the estimated baseline risk of discontinuation of sertraline and escitalopram for less and more severe depression, respectively, and assuming that discontinuation due to side effects is independent of depressive symptom severity. Probability distribution based on assumption.
Response and remission in completers – GP care			
Less severe depression – response More severe depression – response More severe depression – remission Hazards ratios of the above states versus 12-month baseline probability of recovery were estimated using the probabilities	0.57 0.48 0.39	Based on Weibull parameters (lambda and gamma) for baseline probability of recovery [shown below]	Synthesis of data from Gonzales 1985; Holma 2008; Keller 1981, 1984 & 1992; Mueller 1996; and Skodol 2011, using a Bayesian approach – fixed effects model (see Evidence review C, appendix J)

Input parameter	Deterministic value	Probability distribution	Source of data - comments
below: 12-month response – mild depression – moderate depression – severe depression 12-month remission – mild depression – moderate depression – severe depression	 0.79 0.68 0.73 0.79 0.65 0.55	 Beta: α=235; β=61 Beta: α=265; β=126 Beta: α=233; β=88 Beta: α=235; β=61 Beta: α=252; β=139 Beta: α=176; β=145	Simon 1999. For more severe depression, the mean value of moderate and severe depression was used.
Probability of responders (without remission) moving to remission Markov state			
– more severe depression	0.30	Beta: α=30; β=70	Based on the committee's expert opinion
Proportion of people developing common side effects – SSRIs alone or in combination – SNRIs – TCAs – trazodone – mirtazapine	 0.07 0.09 0.07 0.05 0.06	 Beta: α=1,643; β=21,977 Beta: α=437; β=4,325 Beta: α=52; β=724 Beta: α=57; β=1,143 Beta: α=54; β=847	Anderson 2012
Duration of experiencing common side effects over the model time horizon – SSRIs alone or in combination – SNRIs – TCAs – trazodone – mirtazapine	 1.68 years 1.63 years 2.25 years 2.25 years 2.25 years	 No distribution assumed	Anderson 2012
Probability of moving to specific relapse preventive treatment according to acute treatment received – more severe depression			
Acute AD or combined treatment -> maintenance AD Acute individual CBT, BA ->	0.80	Beta: α=80; β=20	Based on the committee's expert opinion

Input parameter	Deterministic value	Probability distribution	Source of data - comments
maintenance 4 sessions	0.80	Beta: α=80; β=20	
Acute individual non-directive counselling, IPT, PDPT -> Maintenance 4 sessions	0.50	Beta: α=50; β=50	
Acute group CBT -> Maintenance group CBT	0.80	Beta: α=80; β=20	
Acute other psychological or physical treatment -> maintenance group CBT	0.50	Beta: α=50; β=50	
Baseline risk of relapse after a single (first) episode			
Weibull distribution – lambda	0.09	95% CI 0.07 to 0.12	Synthesis of data from Eaton 2008 and Mattison 2007, using a Bayesian approach – fixed effects model
Weibull distribution – gamma	0.63	95% CI 0.52 to 0.75	
Hazard ratio – new vs previous episode	1.15	Log-normal: 95% CI 1.11 to 1.18	Kessing 1999
Baseline probability of recovery			Synthesis of data from Gonzales 1985; Holma 2008; Keller 1981, 1984 & 1992; Mueller 1996; Skodol 2011; Stegenga 2012, using a Bayesian approach – fixed effect model
Weibull distribution – lambda	1.16	95% CI 1.08 to 1.24	
Weibull distribution – gamma	0.42	95% CI 0.38 to 0.47	
Mortality			
Risk ratio – depressed vs non-depressed	1.52	Log-normal: 95% CI 1.45 to 1.59	Cuijpers 2014
Baseline mortality – non-depressed	Age/sex specific	No distribution	General mortality statistics for the UK population (Office for National Statistics 2020)
Utility values			
Less severe depression	0.60	Beta: α=182; β=122	Distributions determined using method of moments, based on data reported in Sapin 2004, Sullivan 2004, Sobocki 2006 & 2007, and further assumptions
More severe depression	0.42	Beta: α=54; β=75	
Remission	0.85	Beta: α=923; β=163	
Response not reaching remission	0.72	Beta: α=123; β=48	
Decrement in utility due to side effects	0.09	Beta: α=6; β=59	
Remission state in Markov component	0.81	Beta: α=531; β=125	
Intervention costs – resource use			Probabilities assigned to numbers of sessions

Input parameter	Deterministic value	Probability distribution	Source of data - comments
COMPLETERS			
Number of GP contacts – drug treatment			
- Acute treatment	4	0.70: 4, 0.30: 2-3	Number of visits based on the committee's expert opinion; probabilities based on assumption. If number of GP visits in 2nd year of maintenance pharmacological treatment was lower than 3, only 50% of the drug acquisition cost was incurred and 50% of annual GP contacts due to side effects were made
- 1st year continuation / maintenance	6	0.70: 6, 0.20: 4-5, 0.10: 2-3	
- 2nd year maintenance	3	0.70: 3, 0.30: 1-2	
- Tapering	3	0.70: 3, 0.30: 1-2	
- Discontinuation due to side effects	1	0.80: 1, 0.20: 0	
- Side effects – every 3 months	1	No distribution assigned	
Number of GP contacts – GP care			
- Acute treatment	4	0.50: 4, 0.50: 2-3	
- 1st year maintenance	3	0.70: 3, 0.20: 1-2, 0.10: 0	
- 2nd year maintenance	1	0.70: 1, 0.30: 0	
Number of GP contacts – psych therapy			
- Acute treatment	1	No distribution	
- Maintenance treatment	2	0.60: 2, 0.40: 1	
Psychological interventions - number of sessions			Details on costs of psychological interventions (duration of sessions, type of therapists delivering interventions, and number of participants per group in group therapies) are provided in Table 91. For cCBT without support and cCBT with support one extra initial set-up contact added. For individual problem solving 1 extra initial longer visit added. Participants missing one or more group sessions assumed not to be replaced by others; therefore there was no impact on number of sessions and the total intervention cost.
- cCBT without support	0	No distribution	
- cCBT with support	7	0.70: 7, 0.20: 5-6, 0.10: 4	
- BA individual – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- BA group – less severe depression	8	No distribution	
- CBT individual – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- CBT group – less severe depression	8	No distribution	
- Problem solving – less severe depression	5	0.70: 5, 0.20: 4, 0.10: 3	
- Counselling – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- IPT – less severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- Short-term PDPT – less severe depression	12	0.70: 12, 0.20: 9-11, 0.10: 7-8	
- MBCT (group) – less severe depression	8	No distribution	
- BA individual – more severe depression	12	0.70: 12, 0.20: 9-11, 0.10: 7-8	

Input parameter	Deterministic value	Probability distribution	Source of data - comments
- CBT individual – more severe depression	16	0.70: 16, 0.20: 12-15, 0.10: 9-11	Number of visits based on RCTs included in the NMAs that informed the economic analysis modified by the committee's expert opinion; probabilities based on assumption.
- CBT group – more severe depression	10	No distribution	
- Problem solving – more severe depression	8	0.70: 8, 0.20: 6-7, 0.10: 5	
- Counselling – more severe depression	12	0.70: 12, 0.20: 9-11, 0.10: 7-8	
- IPT – more severe depression	16	0.70: 16, 0.20: 12-15, 0.10: 9-11	
- Short-term PDPT – more severe depression	16	0.70: 16, 0.20: 12-15, 0.10: 9-11	
Physical interventions - number of sessions			Details on costs of physical interventions (duration of sessions, type of therapists delivering interventions, and number of participants per group in group therapies are provided in Table 93. Participants missing one or more group sessions assumed not to be replaced by others; therefore there was no impact on number of sessions and the total intervention cost. Number of visits based on RCTs included in the NMAs that informed the economic analysis modified by the committee's expert opinion; probabilities based on assumption.
- Exercise individ – less severe depression	25	0.70: 25, 0.20: 20-24, 0.10: 15-19	
- Exercise group – less severe depression	30	No distribution	
- Exercise individ – more severe depression	30	0.70: 30, 0.20: 23-29, 0.10: 16-22	
- Exercise group – more severe depression	40	No distribution	
- Acupuncture – more severe depression	25	0.70: 25, 0.20: 20-24, 0.10: 15-19	
Maintenance psychological therapies – number of sessions			Details on costs of maintenance psychological therapies are provided in Table 94.
MBCT (group)	12	No distribution	
CBT group	8	No distribution	
4 individual sessions	4	0.60: 4, 0.40: 2-3	
DISCONTINUERS (acute treatment)			
Number of GP contacts – drug treatment or GP care	1	No distribution	One pack of drugs assumed to be consumed by those discontinuing acute drug treatment
Number of GP contacts – psych therapy	1	No distribution	
Number of psychological intervention sessions			For psychological and physical interventions: initial GP visit added
- cCBT without support	0	No distribution	For cCBT without support and cCBT with support: 1 extra initial set-up contact assumed.

Input parameter	Deterministic value	Probability distribution	Source of data - comments
- cCBT with support	1	No distribution	For individual problem solving: 1 extra initial longer visit assumed. People discontinuing group psychological therapies or exercise were assumed to incur the full cost of therapy
- BA individual – less severe depression	2	No distribution	
- BA group – less severe depression	8	No distribution	
- CBT individual – less severe depression	2	No distribution	
- CBT group – less severe depression	8	No distribution	
- Problem solving – less severe depression	1	No distribution	
- Counselling – less severe depression	2	No distribution	
- IPT – less severe depression	2	No distribution	
- Short-term PDPT – less severe depression	3	No distribution	
- MBCT (group) – less severe depression	8	No distribution	
- BA individual – more severe depression	3	No distribution	
- CBT individual – more severe depression	4	No distribution	
- CBT group – more severe depression	10	No distribution	
- Problem solving – more severe depression	2	No distribution	
- Counselling – more severe depression	3	No distribution	
- IPT – more severe depression	4	No distribution	
- Short-term PDPT – more severe depression	4	No distribution	
Number of physical intervention sessions			
- Exercise individ – less severe depression	7	No distribution	
- Exercise group – less severe depression	30	No distribution	
- Exercise individ – more severe depression	8	No distribution	
- Exercise group – more severe depression	40	No distribution	
- Acupuncture – more severe depression	7	No distribution	
Intervention costs - unit costs (2020 price)			
Drug acquisition costs	Table 86	No distribution	NHS Business Services Authority 2021
Medication for management of side effects	£2.50	No distribution	Assumption – 3-month cost
LFT	£3.07	No distribution	Akhtar 2014
ECG machine and disposables	£3.28	No distribution	National Clinical Guidelines Centre 2016
cCBT provider, hardware & capital overheads	£53	No distribution	Committee's expert advice and Kaltenthaler 2006
Disposable needles per acupuncture session	£1	No distribution	Assumption

Input parameter	Deterministic value	Probability distribution	Source of data - comments
GP	£39	Normal, SE=0.05*mean	Curtis 2020; distribution based on assumption
HI therapist Band 7	£110	Normal, SE=0.05*mean	See Table 89; distribution based on assumption
Therapist Band 6	£89	Normal, SE=0.05*mean	See Table 90; distribution based on assumption
HI MBCT therapist Band 7	£112	Normal, SE=0.05*mean	See Table 89; distribution based on assumption
MBCT therapist Band 6	£91	Normal, SE=0.05*mean	See Table 90; distribution based on assumption
PWP (Band 5)	£50	Normal, SE=0.05*mean	See Table 88; distribution based on assumption
Physiotherapist band 6	£71	Normal, SE=0.05*mean	Curtis 2020, see Table 92; distribution based on assumption
Practice nurse band 5 [delivering ECG]	£51	Normal, SE=0.05*mean	Curtis 2020, taking into account ratio of direct to indirect time
Annual NHS health state cost (2020 price)		Gamma	
Relapse - remaining in state	£1,601	SE=0.20*mean	Based primarily on cost data reported in Byford 2011 supplemented with data from Radhakrishnan 2013, Curtis 2020, NHS England 2016, expressed in 2020 prices using the HCHS inflation index up to year 2016 and then the NHS cost inflation index up to year 2020 (Curtis 2020). Distribution based on assumption
Relapse - final year before remission	£1,165	SE=0.20*mean	
Remission	£533	SE=0.20*mean	
Remission – 1st year extra cost	£206	SE=0.20*mean	
Cost of treatment after discontinuation	£246	SE=0.20*mean	
Annual discount rate	0.035	No distribution	Applied to both costs and outcomes (NICE 2014)

AD: antidepressant; BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; ECG: electrocardiogram; HI: ihigh ntensity; IPT: interpersonal psychotherapy; LFT: liver function test; MBCT: mindfulness-based cognitive therapy; PDPT: psychodynamic psychotherapy; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TAU: treatment as usual; TCAs: tricyclic antidepressants

Presentation of the results

Results are reported separately for each population examined in the economic model. In each analysis, mean intervention costs, total costs and QALYs are presented for each intervention, averaged across 10,000 iterations of the model. For each treatment option, the Net Monetary Benefit (NMB) has been estimated for each iteration and averaged across the 10,000 iterations, determined by the formula

$$NMB = E \bullet \lambda - C$$

where E and C are the effects (QALYs) and total costs, respectively, of each treatment option, and λ represents the moneterised value of each QALY, set at the NICE lower cost-effectiveness threshold of £20,000/QALY (NICE, 2014). The treatment with the highest NMB is the most cost-effective option (Fenwick 2001).

Incremental mean costs and effects (QALYs) of each treatment option versus GP care are also presented in the form of cost effectiveness planes.

The mean (95%CI) ranking by cost-effectiveness is reported for each treatment (out of 10,000 iterations), where a rank of 1 suggests that a treatment is the most cost-effective amongst all evaluated treatment options. Finally, the cost-effectiveness acceptability frontier (CEAF) has been plotted, showing the treatment with the highest mean NMB over different cost-effectiveness thresholds (λ), and the probability that this treatment is the most cost-effective among those assessed (Fenwick 2001).

Validation of the economic model

The economic model (including the conceptual model and the identification and selection of input parameters) was developed by the health economist in collaboration with a health economics sub-group formed by members of the committee. The validity of the model structure, assumptions and input parameters were confirmed by the committee. As part of the model validation, all inputs and model formulae were systematically checked; the model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The base-case results and results of sensitivity analyses were discussed with the committee to confirm their plausibility. In addition, the economic model (excel spreadsheet) and this appendix were checked for their validity and accuracy by a health economist that was external to the guideline development team.

Economic modelling results

Adults with less severe depression

The results of the economic analysis are provided in Table 98. This table shows interventions ordered from the most to the least cost-effective and provides mean QALYs and mean intervention and total costs for each intervention, mean NMBs and rankings by cost effectiveness (with higher NMBs and lower rankings indicating higher cost-effectiveness). Intervention costs include costs for treatment completers and costs for those who discontinued treatment. According to the results, CBT group appeared to be the most cost-effective intervention, followed by BA group, exercise group, sertraline, MBCT group, cCBT without or with minimal support, lofepramine, cCBT with support, CBT individual, BA individual, problem solving individual, IPT, GP care, non-directive counselling, short-term PDPT, and exercise individual. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

Table 98. Results of economic analysis: interventions for adults with a new episode of less severe depression

Intervention	Mean per person				Mean rank (95% CI)
	NMB	QALYs	Intervention cost	Total cost	
CBT group	£32,900	1,731	£337,653	£1,711,356	2.61 (1 to 12)
BA group	£32,622	1,719	£337,653	£1,764,595	5.06 (1 to 14)
Exercise group	£32,501	1,709	£225,146	£1,679,809	5.48 (1 to 13)
Sertraline	£32,420	1,707	£108,286	£1,719,661	6.17 (1 to 14)
MBCT group	£32,370	1,713	£444,276	£1,885,364	7.35 (2 to 15)
cCBT	£32,328	1,697	£117,009	£1,618,769	6.96 (2 to 13)
Lofepramine	£32,272	1,707	£177,443	£1,876,104	7.86 (1 to 15)
cCBT with support	£32,271	1,697	£173,726	£1,675,563	7.47 (1 to 16)
CBT individual	£32,255	1,719	£710,808	£2,119,240	8.08 (3 to 15)
BA individual	£32,233	1,718	£724,433	£2,133,287	8.10 (1 to 16)
Problem solving individual	£31,928	1,683	£170,092	£1,728,566	11.04 (3 to 16)
IPT	£31,883	1,701	£636,945	£2,129,449	12.01 (5 to 16)
GP care	£31,871	1,676	£94,525	£1,651,096	11.96 (4 to 16)
Non-directive counselling	£31,770	1,699	£733,336	£2,210,591	10.27 (2 to 16)
Short-term PDPT	£31,731	1,713	£1,113,482	£2,534,599	11.94 (3 to 16)
Exercise individual	£31,668	1,707	£1,013,382	£2,467,523	13.63 (8 to 16)

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy

Figure 64 provides the cost effectiveness plane of the analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with GP care (TAU), which is placed at the origin. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that non-directive counselling, short-term PDPT, and individual exercise may be less cost-effective than with GP care at this threshold (since they all lie on the left side of the dotted line).

The CEAF of the analysis is shown in Figure 65. It can be seen that cCBT is the most cost-effective option at a cost-effectiveness threshold between zero and £2,500/QALY, with a rather low probability that reaches 0.37 at zero cost effectiveness threshold and then drops down to 0.23. For higher cost-effectiveness thresholds, CBT group is the most cost-effective option, with a probability of cost effectiveness that starts at 0.30 and reaches 0.58 at a cost effectiveness threshold of £40,000/QALY.

Figure 64. Cost effectiveness plane of interventions for the treatment of a new episode of less severe depression in adults plotted against GP care (reference treatment reflected in TAU) – incremental costs and QALYs versus GP care per 1,000 adults with less severe depression

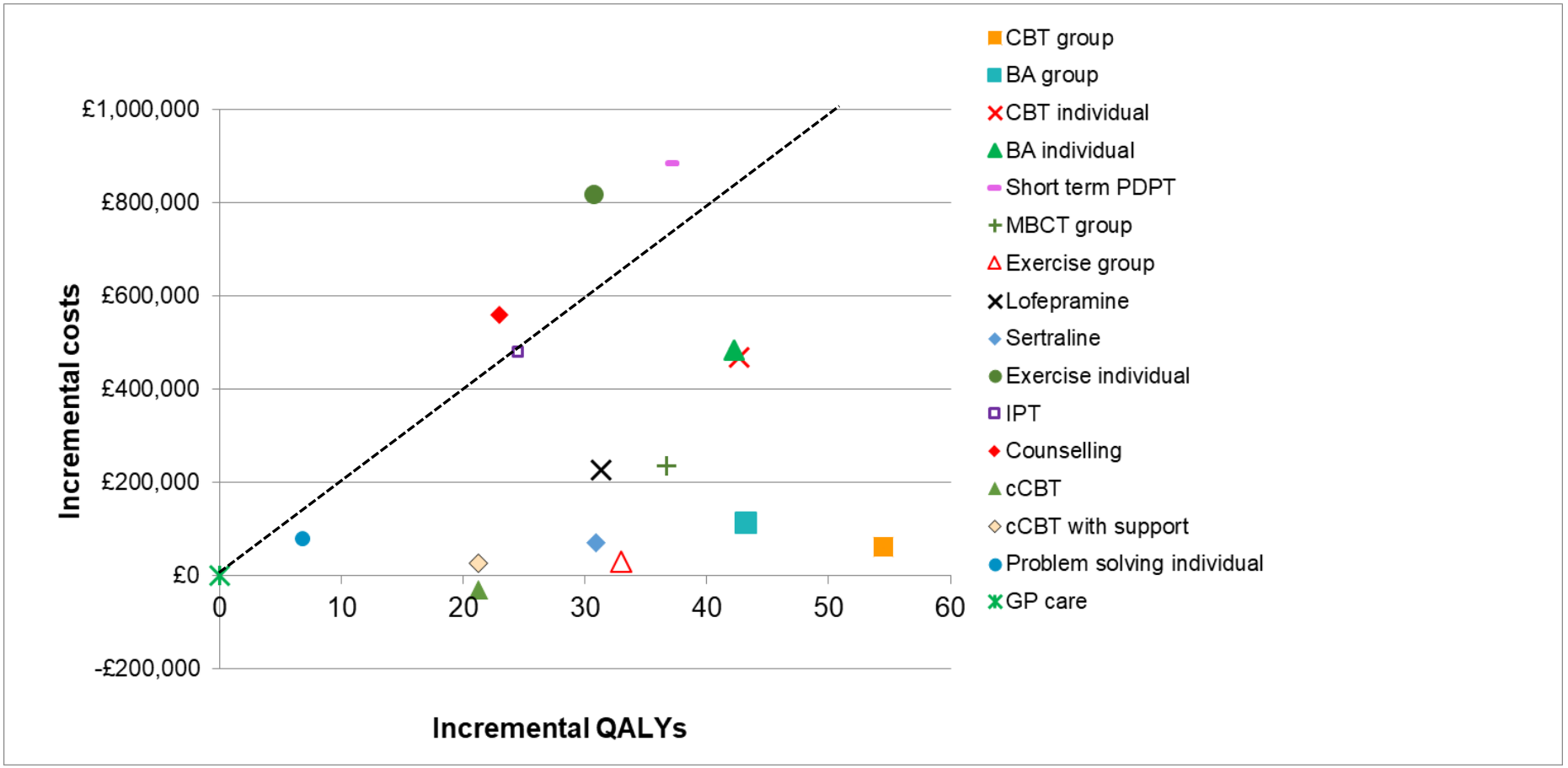
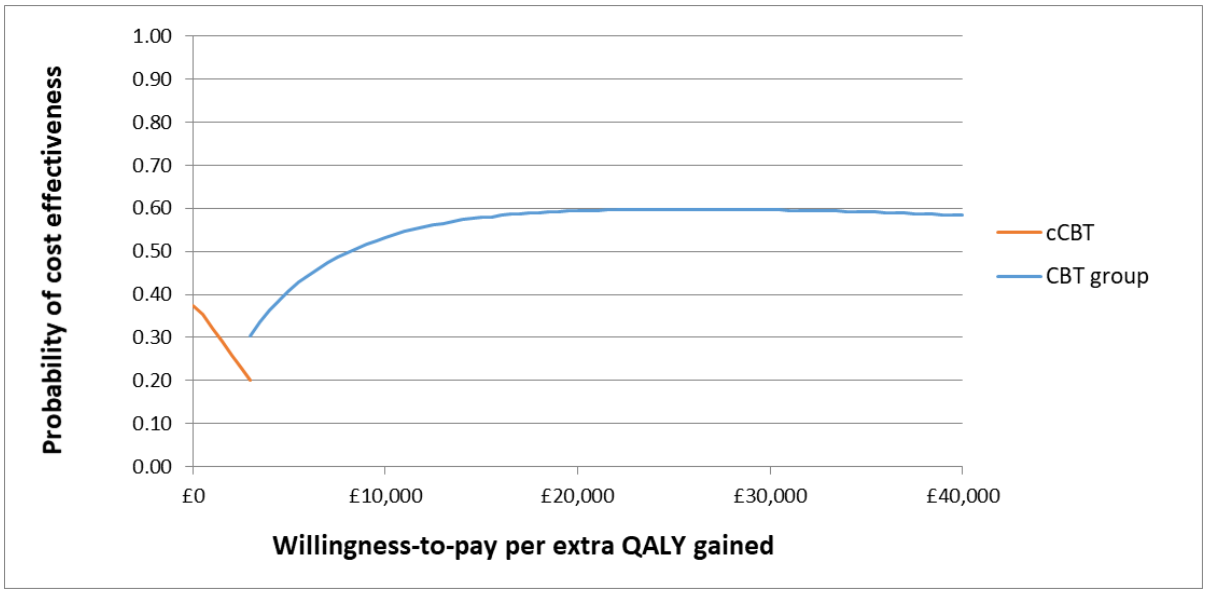


Figure 65 Cost-effectiveness acceptability frontier of interventions for the treatment of a new episode of less severe depression in adults



Results were overall robust to the scenarios explored through deterministic sensitivity analysis (Table 99) with small changes in the ranking of interventions. When the number of sessions of group psychological interventions was doubled, the relative cost-effectiveness of MBCT and, to a lesser degree, group BA, was reduced; however, group CBT remained the most cost-effective intervention. The impact of changes in the number of sessions of individual high-intensity psychological interventions was less profound. The cost-effectiveness of pharmacological interventions was reduced when the risk of developing side effects was increased.

Table 99. Results of deterministic sensitivity analysis – adults with less severe depression

Base-case deterministic analysis		Increase in the number of previous episodes (2 from 0)		Utility values from Mann 2009		Utility values from Koeser 2015 / Kolovos 2017		50% reduction in the cost of a depressive episode		50% increase in cost of depressive episode	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
CBT group	£33,114	CBT group	£33,003	CBT group	£32,841	CBT group	£32,773	CBT group	£33,238	CBT group	£32,989
BA group	£32,801	BA group	£32,696	BA group	£32,841	BA group	£32,485	BA group	£32,966	BA group	£32,635
Exercise group	£32,701	Exercise group	£32,600	Exercise group	£32,841	Exercise group	£32,405	Exercise group	£32,899	Exercise group	£32,503
MBCT group	£32,592	MBCT group	£32,489	MBCT group	£32,841	MBCT group	£32,287	MBCT group	£32,774	MBCT group	£32,410
cCBT	£32,456	cCBT	£32,362	cCBT	£32,841	cCBT	£32,190	cCBT	£32,702	BA individual	£32,253
Sertraline	£32,453	Sertraline	£32,357	cCBT with support	£32,841	cCBT with support	£32,175	cCBT with support	£32,684	Sertraline	£32,248
cCBT with support	£32,445	cCBT with support	£32,351	Sertraline	£32,841	Sertraline	£32,162	Sertraline	£32,658	cCBT	£32,209
BA individual	£32,407	BA individual	£32,300	BA individual	£32,841	BA individual	£32,084	BA individual	£32,560	cCBT with support	£32,207
CBT individual	£32,359	CBT individual	£32,254	CBT individual	£32,841	CBT individual	£32,042	CBT individual	£32,522	CBT individual	£32,196
Lofepramine	£32,313	Lofepramine	£32,216	Lofepramine	£32,841	Lofepramine	£32,015	Lofepramine	£32,508	Lofepramine	£32,118
Counselling	£32,080	Counselling	£31,980	Problem solving	£32,841	Counselling	£31,785	Counselling	£32,279	Counselling	£31,881
Problem solving	£31,964	Problem solving	£31,878	Counselling	£32,841	Problem solving	£31,734	Problem solving	£32,268	Short-term PDPT	£31,769
Short-term PDPT	£31,930	Short-term PDPT	£31,824	GP care	£32,841	IPT	£31,643	GP care	£32,181	IPT	£31,683
IPT	£31,917	IPT	£31,821	IPT	£32,841	GP care	£31,634	IPT	£32,150	Problem solving	£31,659
GP care	£31,845	GP care	£31,764	Short-term PDPT	£32,841	Short-term PDPT	£31,611	Short-term PDPT	£32,090	Exercise individual	£31,521
Exercise individual	£31,726	Exercise individual	£31,627	Exercise individual	£32,841	Exercise individual	£31,435	Exercise individual	£31,931	GP care	£31,509
20% reduction in baseline discontinuation		**20% increase in baseline discontinuation**		**100% self-referral to psychological therapies**		**All HI individual psych interventions delivered in 8 sessions; group psych intervention sessions doubled**		**HI individual psych interventions delivered in 12 sessions; group psych intervention sessions doubled**		**40% risk of developing side effects from antidepressants**	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
CBT group	£33,212	CBT group	£33,004	CBT group	£33,153	CBT group	£32,815	CBT group	£32,815	CBT group	£33,114
BA group	£32,930	BA group	£32,666	BA group	£32,840	Exercise group	£32,701	Exercise group	£32,701	BA group	£32,801
Exercise group	£32,772	Exercise group	£32,622	Exercise group	£32,701	BA group	£32,502	BA group	£32,502	Exercise group	£32,701
MBCT group	£32,671	MBCT group	£32,503	MBCT group	£32,631	cCBT	£32,456	cCBT	£32,456	MBCT group	£32,592
Sertraline	£32,548	cCBT	£32,392	cCBT	£32,495	Sertraline	£32,453	Sertraline	£32,453	cCBT	£32,456
cCBT	£32,514	cCBT with support	£32,383	cCBT with support	£32,475	cCBT with support	£32,445	cCBT with support	£32,445	cCBT with support	£32,445
cCBT with support	£32,503	BA individual	£32,378	Sertraline	£32,453	BA individual	£32,407	Lofepramine	£32,313	BA individual	£32,407
BA individual	£32,430	Sertraline	£32,359	BA individual	£32,442	CBT individual	£32,359	MBCT group	£32,187	CBT individual	£32,359

Lofepramine	£32,427	CBT individual	£32,322	CBT individual	£32,393	Short-term PDPT	£32,339	BA individual	£32,008	Counselling	£32,080
CBT individual	£32,391	Lofepramine	£32,203	Lofepramine	£32,313	Lofepramine	£32,313	CBT individual	£31,977	Sertraline	£32,018
Counselling	£32,095	Counselling	£32,063	Counselling	£32,116	MBCT group	£32,187	Problem solving	£31,964	Problem solving	£31,964
Problem solving	£31,987	Problem solving	£31,939	Problem solving	£31,992	Counselling	£32,080	Short-term PDPT	£31,930	Short-term PDPT	£31,930
IPT	£31,947	Short-term PDPT	£31,918	Short-term PDPT	£31,966	Problem solving	£31,964	GP care	£31,845	IPT	£31,917
Short-term PDPT	£31,940	IPT	£31,885	IPT	£31,946	IPT	£31,917	Exercise individual	£31,726	Lofepramine	£31,889
GP care	£31,848	GP care	£31,842	GP care	£31,845	GP care	£31,845	Counselling	£31,682	GP care	£31,845
Exercise individual	£31,738	Exercise individual	£31,712	Exercise individual	£31,726	Exercise individual	£31,726	IPT	£31,592	Exercise individual	£31,726

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; HI: high intensity; IPT: interpersonal psychotherapy; MBCT: mindfulness-based cognitive therapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy; psych: psychological; PWP: psychological well-being practitioner

Adults with more severe depression

The unadjusted results of the economic analysis are provided in Table 100. The results of the probabilistic bias-adjusted analysis that utilised data on discontinuation and response in completers from the respective bias NMA models are shown in Table 101. Interventions have been ordered from the most to the last cost-effective. The tables provide the mean QALYs and mean intervention and total costs for each intervention, mean NMBs and rankings by cost effectiveness (with higher NMBs and lower rankings indicating higher cost-effectiveness). Intervention costs include costs for treatment completers and costs for those who discontinued treatment.

According to the bias-adjusted results, individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

Table 100. Results of unadjusted economic analysis: interventions for adults with a new episode of more severe depression

Intervention	Mean per person				Mean rank (95% CI)
	NMB	QALYs	Intervention cost	Total cost	
Individual problem solving	£28,967	1,554	£242,818	£2,104,317	2.05 (1 to 10)
CBT individual + escitalopram	£28,073	1,565	£1,418,661	£3,224,319	6.39 (1 to 17)
Duloxetine	£27,989	1,501	£110,823	£2,038,483	5.97 (2 to 10)
cCBT with support	£27,952	1,502	£176,303	£2,090,004	7.15 (1 to 17)
Mirtazapine	£27,950	1,498	£107,574	£2,019,872	6.62 (2 to 12)
BA individual	£27,944	1,542	£1,070,325	£2,896,732	7.14 (1 to 17)
Exercise group	£27,868	1,503	£287,131	£2,199,976	7.77 (2 to 16)
Escitalopram	£27,833	1,493	£108,101	£2,023,604	8.24 (4 to 13)
Lofepramine	£27,823	1,503	£188,176	£2,232,436	8.06 (2 to 16)
Acupuncture + escitalopram	£27,804	1,524	£796,277	£2,681,709	8.77 (1 to 18)
Trazodone	£27,598	1,482	£102,704	£2,040,012	10.89 (6 to 15)
CBT individual	£27,556	1,538	£1,375,691	£3,206,707	10.96 (4 to 17)
CBT group	£27,302	1,482	£412,549	£2,329,921	12.39 (2 to 19)
cCBT	£27,194	1,463	£116,960	£2,072,382	12.07 (1 to 20)
Non-directive counselling	£26,998	1,497	£1,022,816	£2,939,938	14.42 (3 to 20)
IPT	£26,951	1,513	£1,419,832	£3,314,372	14.83 (4 to 20)
Exercise individual	£26,887	1,493	£1,054,538	£2,980,498	15.47 (6 to 20)
GP care	£26,865	1,439	£87,557	£1,910,907	16.15 (12 to 19)
Short-term PDPT	£26,703	1,494	£1,254,238	£3,171,873	15.92 (5 to 20)
Acupuncture	£25,873	1,430	£724,128	£2,718,558	18.77 (12 to 20)

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy

Table 101. Results of bias-adjusted economic analysis: interventions for people with a new episode of more severe depression

Intervention	Mean per person				Mean rank (95% CI)
	NMB	QALYs	Intervention cost	Total cost	
Individual problem solving	£28,929	1,552	£243,567	£2,108,870	1.85 (1 to 9)
CBT individual + escitalopram	£27,947	1,558	£1,402,841	£3,219,785	6.18 (1 to 16)
Duloxetine	£27,911	1,498	£110,867	£2,043,891	5.24 (2 to 9)
Mirtazapine	£27,824	1,493	£107,606	£2,027,931	6.48 (2 to 12)
BA individual	£27,768	1,534	£1,072,316	£2,910,213	7.28 (1 to 18)
Escitalopram	£27,746	1,489	£108,290	£2,029,963	7.52 (4 to 12)
Acupuncture + escitalopram	£27,735	1,520	£780,179	£2,672,040	8.08 (1 to 17)
Exercise group	£27,702	1,496	£287,188	£2,209,098	7.81 (2 to 17)
Lofepramine	£27,689	1,496	£187,942	£2,236,393	7.91 (2 to 15)
Trazodone	£27,507	1,478	£103,309	£2,046,731	10.17 (5 to 15)
cCBT with support	£27,488	1,480	£176,015	£2,114,443	9.39 (1 to 19)
CBT individual	£27,309	1,526	£1,353,628	£3,201,785	11.50 (4 to 17)
CBT group	£26,952	1,465	£412,310	£2,349,604	13.51 (2 to 20)
Non-directive counselling	£26,934	1,493	£1,012,410	£2,934,391	13.63 (3 to 20)
GP care	£26,868	1,439	£89,097	£1,911,976	14.94 (11 to 18)
cCBT	£26,797	1,445	£117,009	£2,094,139	13.17 (1 to 20)
IPT	£26,575	1,495	£1,410,358	£3,326,426	15.52 (5 to 20)
Short-term PDPT	£26,554	1,486	£1,231,776	£3,159,256	15.56 (5 to 20)
Exercise individual	£26,504	1,475	£1,044,561	£2,990,588	15.84 (7 to 20)
Acupuncture	£25,758	1,425	£738,364	£2,738,737	18.43 (11 to 20)

BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy

Figure 66 provides the cost-effectiveness plane of the bias-adjusted analysis. Each intervention is placed on the plane according to its incremental costs and QALYs compared with GP care (placebo), which is placed at the origin. The slope of the dotted line indicates the NICE lower cost effectiveness threshold, suggesting that cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture may be less cost-effective than GP care at this threshold.

The CEAF of the analysis is shown in Figure 67. It can be seen that GP care is the most cost-effective option at cost effectiveness thresholds up to £2,500/QALY, with a probability that reaches 0.94 at a zero cost effectiveness threshold, which then drops down to 0.27. For higher cost-effectiveness thresholds, individual problem solving is the most cost-effective option for the treatment of more severe depressive episodes, with a probability of cost effectiveness that starts at 0.43, reaches its highest probability of 0.78 at a cost-effectiveness threshold of £10,000/QALY, and then falls at 0.56 at a cost effectiveness threshold of £40,000/QALY.

Figure 66. Cost-effectiveness plane of interventions for the treatment of a new episode of more severe depression in adults plotted against GP care (placebo) – incremental costs and QALYs versus GP care per 1,000 adults with more severe depression, bias-adjusted analysis

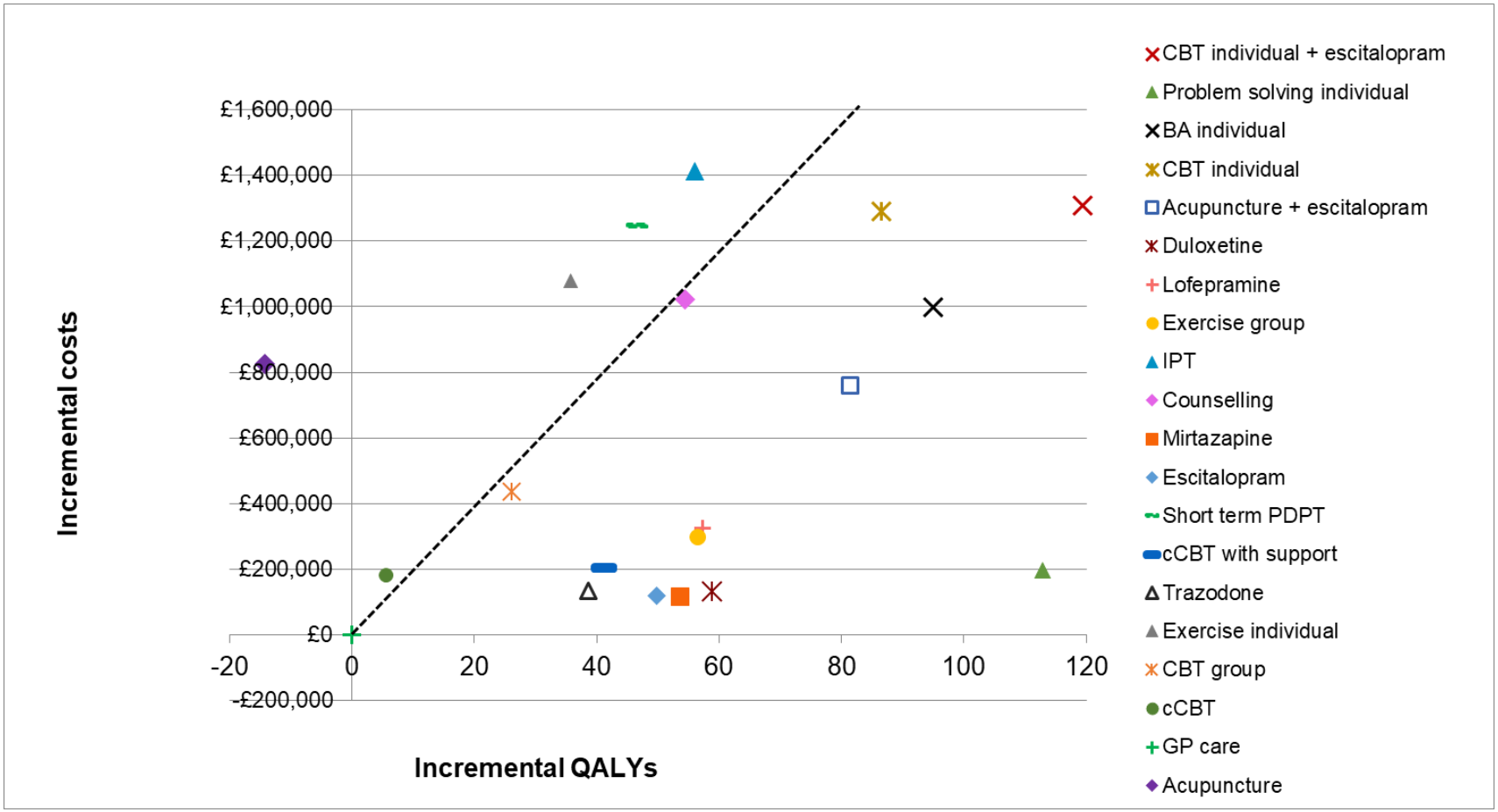
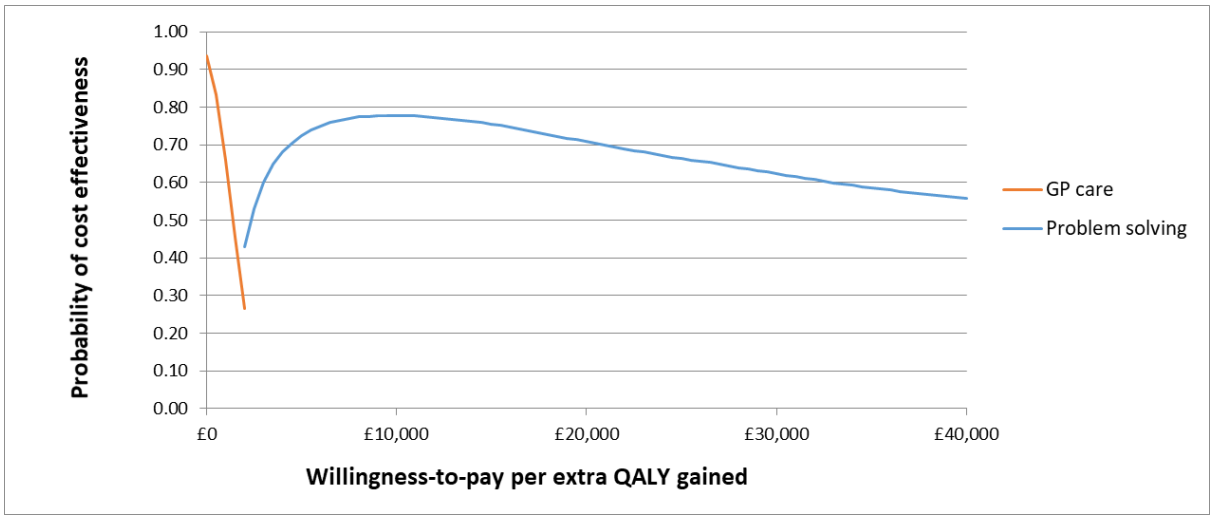


Figure 67. Cost-effectiveness acceptability frontier of interventions for the treatment of a new episode of more severe depression in adults – bias-adjusted analysis



Results were overall robust to alternative scenarios tested in one-way deterministic sensitivity analysis (Table 102), with the following exceptions: when the higher utility value from Mann 2009 was attached to more severe depression (translating into a more limited scope for HRQoL improvement following successful treatment), the relative cost-effectiveness of combined and high intensity psychological interventions was greatly reduced; all high intensity psychological interventions became less cost-effective than GP care and the rankings of pharmacological interventions and cCBT with support were substantially improved. Also, when the risk of developing side effects from antidepressants was increased (40%), the cost-effectiveness of pharmacological and combined interventions was reduced.

Table 102. Results of deterministic sensitivity analysis – adults with more severe depression, bias-adjusted analysis

Bias-adjusted, base-case deterministic analysis		Increase in the number of previous episodes (5 from 2)		Utility values from Mann 2009		Utility values from Koeser 2015 / Kolovos 2017		50% reduction in the cost of a depressive episode		50% increase in cost of depressive episode	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
Problem solving	£29,066	Problem solving	£28,728	Problem solving	£30,745	Problem solving	£28,792	Problem solving	£29,431	Problem solving	£28,701
CBT indiv + escit	£28,084	CBT indiv + escit	£27,853	Duloxetine	£29,972	CBT indiv + escit	£27,818	CBT indiv + escit	£28,405	CBT indiv + escit	£27,764
Duloxetine	£27,908	Duloxetine	£27,699	Exercise group	£29,932	Duloxetine	£27,696	Duloxetine	£28,361	Duloxetine	£27,456
Exercise group	£27,857	Mirtazapine	£27,616	Mirtazapine	£29,930	Exercise group	£27,628	Exercise group	£28,322	Exercise group	£27,392
Mirtazapine	£27,822	Exercise group	£27,565	cCBT with support	£29,909	Mirtazapine	£27,613	Mirtazapine	£28,286	Mirtazapine	£27,357
cCBT with support	£27,745	Escitalopram	£27,535	Escitalopram	£29,878	cCBT with support	£27,545	cCBT with support	£28,222	Acupunct + escit	£27,301
Escitalopram	£27,738	Acupunct + escit	£27,510	Lofepramine	£29,768	Escitalopram	£27,534	Escitalopram	£28,210	cCBT with support	£27,268
Acupunct + escit	£27,719	Lofepramine	£27,492	Trazodone	£29,741	Lofepramine	£27,484	Lofepramine	£28,152	Escitalopram	£27,266
Lofepramine	£27,697	cCBT with support	£27,460	CBT indiv + escit	£29,637	Acupunct + escit	£27,456	Acupunct + escit	£28,137	Lofepramine	£27,242
Trazodone	£27,524	Trazodone	£27,317	Acupunct + escit	£29,586	Trazodone	£27,330	Trazodone	£28,014	Trazodone	£27,033
CBT individual	£27,322	CBT individual	£27,057	GP care	£29,457	CBT individual	£27,091	CBT individual	£27,728	CBT individual	£26,916
BA individual	£27,249	BA individual	£26,997	CBT group	£29,399	BA individual	£27,036	BA individual	£27,685	BA individual	£26,814
CBT group	£27,100	CBT group	£26,828	cCBT	£29,333	CBT group	£26,905	CBT group	£27,618	CBT group	£26,583
GP care	£26,950	GP care	£26,700	BA individual	£29,259	GP care	£26,786	GP care	£27,516	Counselling	£26,457
Counselling	£26,932	Counselling	£26,679	CBT individual	£29,206	Counselling	£26,703	Counselling	£27,407	GP care	£26,384
cCBT	£26,846	cCBT	£26,600	Counselling	£29,038	cCBT	£26,684	cCBT	£27,404	cCBT	£26,288
Exercise individual	£26,740	Short-term PDPT	£26,475	Exercise individual	£28,911	Exercise individual	£26,519	Exercise individual	£27,232	Short-term PDPT	£26,263
Short-term PDPT	£26,734	Exercise individual	£26,461	Short-term PDPT	£28,838	Short-term PDPT	£26,511	Short-term PDPT	£27,205	Exercise individual	£26,249
IPT	£26,692	IPT	£26,432	IPT	£28,759	IPT	£26,485	IPT	£27,143	IPT	£26,241
Acupuncture	£26,074	Acupuncture	£25,832	Acupuncture	£28,596	Acupuncture	£25,916	Acupuncture	£26,640	Acupuncture	£25,507
20% reduction in baseline discontinuation		**20% increase in baseline discontinuation**		**100% self-referral to psychological therapies**		**All HI individual psych interventions delivered in 12 sessions; group psych intervention sessions doubled**		**All HI individual psych interventions delivered in 16 sessions; group psych intervention sessions doubled**		**40% risk of developing side effects from antidepressants**	
Intervention	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**	**Intervention**	**NMB**
Problem solving	£29,197	Problem solving	£28,924	Problem solving	£29,097	Problem solving	£29,066	Problem solving	£29,066	Problem solving	£29,066
CBT indiv + escit	£28,227	CBT indiv + escit	£27,938	CBT indiv + escit	£28,112	CBT indiv + escit	£28,401	CBT indiv + escit	£28,084	Exercise group	£27,857
Duloxetine	£28,034	Duloxetine	£27,787	Duloxetine	£27,908	Duloxetine	£27,908	Duloxetine	£27,908	cCBT with support	£27,745
Exercise group	£28,007	Mirtazapine	£27,717	Exercise group	£27,857	Exercise group	£27,857	Exercise group	£27,857	Duloxetine	£27,410

Mirtazapine	£27,929	Exercise group	£27,715	Mirtazapine	£27,822	Mirtazapine	£27,822	Mirtazapine	£27,822	CBT indiv + esci	£27,330
Escitalopram	£27,832	cCBT with support	£27,661	cCBT with support	£27,772	cCBT with support	£27,745	cCBT with support	£27,745	CBT individua	£27,322
cCBT with support	£27,829	Escitalopram	£27,646	Escitalopram	£27,738	Escitalopram	£27,738	Escitalopram	£27,738	Mirtazapin	£27,309
Acupunct + escit	£27,828	Acupunct + escit	£27,610	Acupunct + escit	£27,719	Acupunct + escit	£27,719	Acupunct + escit	£27,719	BA individual	£27,249
Lofepramine	£27,805	Lofepramine	£27,593	Lofepramine	£27,697	Lofepramine	£27,697	Lofepramine	£27,697	Escitalopram	£27,221
Trazodone	£27,617	Trazodone	£27,437	Trazodone	£27,524	CBT individual	£27,646	Trazodone	£27,524	Lofepramine	£27,190
CBT individual	£27,388	CBT individual	£27,255	CBT individual	£27,351	Trazodone	£27,524	CBT individual	£27,322	Acupunct + escit	£27,135
BA individual	£27,289	BA individual	£27,207	BA individual	£27,280	BA individual	£27,249	GP care	£26,950	CBT group	£27,100
CBT group	£27,149	CBT group	£27,052	CBT group	£27,139	IPT	£27,039	BA individual	£26,900	Trazodone	£27,066
Counselling	£26,960	GP care	£26,961	Counselling	£26,961	Short-term PDPT	£27,014	cCBT	£26,846	GP care	£26,950
GP care	£26,939	Counselling	£26,905	GP care	£26,950	GP care	£26,950	Exercise individual	£26,740	Counselling	£26,932
cCBT	£26,847	cCBT	£26,846	cCBT	£26,885	Counselling	£26,932	Short-term PDPT	£26,734	cCBT	£26,846
Exercise individual	£26,767	Exercise individual	£26,717	Short-term PDPT	£26,759	cCBT	£26,846	CBT group	£26,727	Exercise individual	£26,740
Short-term PDPT	£26,763	Short-term PDPT	£26,708	Exercise individual	£26,740	Exercise individual	£26,740	IPT	£26,692	Short-term PDPT	£26,734
IPT	£26,706	IPT	£26,679	IPT	£26,723	CBT group	£26,727	Counselling	£26,611	IPT	£26,692
Acupuncture	£26,030	Acupuncture	£26,121	Acupuncture	£26,074	Acupuncture	£26,074	Acupuncture	£26,074	Acupuncture	£26,074

Acupunct: acupuncture; BA: behavioural activation; CBT: cognitive behavioural therapy; cCBT: computerised cognitive behavioural therapy; escit: escitalopram; HI: high intensity; indiv: individual; IPT: interpersonal psychotherapy; NMB: net monetary benefit; PDPT: psychodynamic psychotherapy; psych: psychological; PWP: psychological well-being practitioner

Discussion – conclusions, strengths and limitations of economic analysis

The guideline economic analysis assessed the cost effectiveness of a range of pharmacological, psychological, physical and combined interventions for the treatment of new depressive episodes in adults with less severe depression and adults with more severe depression treated in primary care. The interventions assessed were determined by the availability of efficacy and acceptability data obtained from the NMAs that were conducted to inform this guideline. Specific interventions were used as exemplars within each class, so that results of interventions can be extrapolated to other interventions of similar effectiveness and resource intensity within their class.

In adults with less severe depression, group CBT appeared to be the most cost-effective intervention, followed by group BA, group exercise, sertraline, group MBCT, cCBT without or with minimal support, lofepramine, and cCBT with support. These were followed by individual CBT, individual BA, individual problem solving, IPT, GP care, non-directive counselling, short-term PDPT, and individual exercise. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

In adults with more severe depression, individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

Results for both populations were characterised by considerable uncertainty, as reflected in the wide 95% credible intervals around their mean rankings. On the other hand, results of the economic analysis were overall robust to different scenarios explored through deterministic sensitivity analysis, especially in the analysis of interventions for the management of a new episode of less severe depression. Attaching higher utility values to the states of less and more severe depression, which reduced the scope for HRQoL improvement following successful treatment had a strong impact on the results for people with more severe depression: under this scenario, the relative cost-effectiveness of combined and high intensity psychological interventions was greatly reduced, all high intensity psychological interventions became less cost-effective than GP care and the rankings of pharmacological interventions and cCBT with support were substantially improved. Increasing the risk of developing side effects from antidepressant medication resulted in a reduction of the relative cost-effectiveness of antidepressants and combined interventions.

The analysis utilised clinical effectiveness parameters derived from NMAs conducted specifically to inform economic modelling. This methodology enabled evidence synthesis from both direct and indirect comparisons between interventions, and allowed simultaneous inference on all treatments examined in pair-wise trial comparisons while respecting randomisation (Lu 2004, Caldwell 2005). The quality and limitations of RCTs considered in the NMAs have unavoidably impacted on the quality of the economic model clinical input parameters. For example, economic results may be have been affected by reporting and publication bias, although bias-adjusted models and respective sensitivity analyses tested the impact of bias relating to small study size on the results of the economic analyses. Some evidence of inconsistency between the direct and indirect evidence was identified for the response in completers outcome in the analyses of less severe depression and for discontinuation, discontinuation due to side effects from medication in those discontinuing treatment, and remission in completers in the analyses for more severe depression. The limitations characterising the data included in the NMAs and the NMA outputs informing the economic analyses should be considered when interpreting the cost effectiveness results.

Each NMA informing the economic analysis assessed a range of psychological, pharmacological, physical or combined interventions. A key assumption when conducting NMA is that the populations included in all RCTs considered in the NMA are similar. However, participants in pharmacological and non-pharmacological (psychological or physical intervention) trials may differ to the extent that some participants find different interventions more or less acceptable in light of their personal circumstances and preferences (so that they might be willing to participate in a pharmacological trial but not a psychological one and vice versa). Similarly, self-help trials may recruit participants who would not seek or accept face-to-face interventions. However, a number of trials included in the NMAs that informed the economic analysis have successfully recruited participants who are willing to be randomised to either pharmacological or psychological intervention and to either self-help or face-to-face treatment. The NMAs have assumed that service users are willing to accept any of the interventions included in the analyses; in practice, treatment decisions may be influenced by individual values and goals, and people's preferences for different types of interventions. These factors were taken into account when interpreting the results of the economic analysis and when formulating recommendations.

Baseline risks (discontinuation, discontinuation due to intolerable side effects, response and remission) were estimated based on a review of naturalistic studies. Available data suggested that recovery over time is characterised by a Weibull distribution, in which the events rates are proportional to a power of time. Estimation of the distribution parameters determined the probability of response and remission at 12 weeks for less and more severe depression, as relevant, based on a study that provided relevant data specific to different levels of depressive symptom severity.

The time horizon of the analysis was 12 weeks of acute treatment plus 2 years of follow up, which included maintenance treatment, as appropriate, for people with more severe depression following response to treatment. This time horizon was considered adequate to capture the full costs and effects of a course of treatment for depression (including acute and, if appropriate, maintenance treatment).

Utility data used in the economic model were derived from a systematic review of studies reporting utility data for depression-related health states that were generated using the EQ-5D and the UK population tariff, as recommended by NICE.

Intervention costs were estimated based on relevant information provided in the studies included in the NMA supplemented by the committee's expert opinion, in order to reflect routine NHS practice. NHS and PSS costs incurred by adults with depression following remission, treatment discontinuation, lack of adequate response or relapse were derived from a large (N=88,935) naturalistic study that aimed to estimate health service use and costs associated with non-remission in people with depression using data from a large primary care UK general practice research database (Byford 2011). Resource estimates and unit costs were updated with 2020 cost data and supplemented with further evidence according to the committee's expert advice, where appropriate, to reflect current routine practice in the UK NHS.

The impact of intolerable side effects that led to treatment discontinuation as well as of other common side effects of pharmacological or combined treatments on HRQoL and costs associated with their management was incorporated in the economic analysis. The analysis utilised data from a large large US managed care claims database. The committee acknowledged that surveys of self-reported side effects in people receiving antidepressant medication report much higher prevalence of side effects, however, evidence suggests that only a proportion of those impact on HRQoL and management costs. The committee pointed out that the focus of the economic analysis was the prevalence of side effects with a measurable impact on HRQoL and healthcare resource use and this was more likely to be reflected in side effects recorded through patient claims. Nevertheless, a sensitivity analysis was conducted, which tested a higher prevalence of side effects from antidepressant

treatment, to explore its impact on cost-effectiveness results. No side effects were considered for people receiving non-pharmacological interventions; however, people receiving non-pharmacological treatments for depression are also expected to experience a range of events such as headaches, nausea or vomiting, etc. Therefore, the economic analysis may have overestimated the impact of common side effects from antidepressants relative to other treatments and thus underestimated their relative cost effectiveness. On the other hand, other less common side effects associated with treatment with antidepressants (such as upper gastrointestinal bleeds and falls) were not considered in the economic model. Such side effects result in considerable reduction in HRQoL and high costs for their management; nevertheless, they are relatively rare and therefore their omission is unlikely to have significantly impacted on the model results, although it is acknowledged as a limitation that has potentially overestimated the cost effectiveness of drugs or combined interventions with a drug component relative to other interventions. On balance, the committee considered that the economic results were not affected by the limitations in capturing costs and disutilities associated with side effects of treatment.

Overall conclusions from the guideline economic analysis

In adults with less severe depression, group CBT appeared to be the most cost-effective intervention, followed by group BA, group exercise, sertraline, group MBCT, cCBT without or with minimal support, lofepramine, and cCBT with support. These were followed by individual CBT, individual BA, individual problem solving, IPT, GP care, non-directive counselling, short-term PDPT, and individual exercise. The probability of CBT group being the most cost-effective option was 0.60 at the NICE lower cost effectiveness threshold of £20,000/QALY.

In adults with more severe depression, individual problem solving appeared to be the most cost-effective intervention, followed by combined individual CBT with escitalopram, duloxetine, mirtazapine, individual BA, escitalopram, acupuncture combined with escitalopram, exercise group, lofepramine, trazodone, cCBT with support, individual CBT, group CBT, non-directive counselling, GP care, cCBT without or with minimal support, IPT, short-term PDPT, individual exercise and acupuncture. The probability of individual problem solving being the most cost-effective option was 0.71 at the NICE lower cost effectiveness threshold of £20,000/QALY.

The results of the analysis were characterised by considerable uncertainty, as reflected in the wide 95% credible intervals (CrI) around the rankings of interventions. On the other hand, deterministic sensitivity analysis suggested that the results and the ranking of interventions from the most to the least cost-effective were overall robust under different scenarios explored.

Conclusions from the guideline economic analysis refer mainly to people with depression who are treated in primary care for a new depressive episode; however, they may be relevant to people in secondary care as well, given that clinical evidence was derived from a mixture of primary and secondary care settings (however, it needs to be noted that costs utilised in the guideline economic model were mostly relevant to primary care).

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Appendix K – Excluded studies

Excluded studies for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Clinical studies

Please refer to supplement B1 - Clinical evidence tables for treatment of a new episode of depression

Economic studies

Please refer to Supporting documentation - Economic evidence included & excluded studies.

Appendix L – Research recommendations

Research recommendations for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Research question

Is peer support an effective and cost-effective intervention in improving outcomes, including symptoms, personal functioning and quality of life in adults as a stand-alone intervention in people with less severe depression and as an adjunct to other evidence-based interventions in more severe depression?

Why this is important

Not all people with depression respond well to first-line treatments and for some people the absence of good social support systems may account for the limited response to first-line interventions. A number of models for the provision of peer support have been developed in mental health which aim to provide direct personal support and help with establishing and maintaining supportive social networks, but to date few studies have established and tested peer support models for people with depression.

Table 103. Research recommendation rationale

Research question	Is peer support an effective and cost-effective intervention in improving outcomes, including symptoms, personal functioning and quality of life in adults as a stand-alone intervention in people with less severe depression and as an adjunct to other evidence-based interventions in more severe depression?
Importance to 'patients' or the population	Depression is a debilitating and highly prevalent condition in adults. Despite significant investment, the most effective and well-established treatments have only modest effects on depressive symptoms, and more effective treatments for acute depression are therefore required.
Relevance to NICE guidance	Peer support is not currently recommended as there is insufficient evidence for its use.
Relevance to the NHS	Peer support may be an effective and cost-effective treatment for depression, and its use may therefore lead to reduced costs for treating people with acute depression.
National priorities	The NHS Five Year Forward plan makes access to effective mental health services a key national priority.
Current evidence base	There is no available evidence to show the effectiveness of peer support.
Equality	No equality issues.
Feasibility	A series of randomised controlled trials would be required to assess the effectiveness of different models of peer support.
Other comments	None

Table 104. Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (18 years or older) with acute episode of depression.

Criterion	Explanation
Intervention	Peer support models, including both individual and group interventions, provided by people who themselves have personal experience of a mental health problem. Peer support for different severities of depression alone or in combination with evidence-based interventions for the treatment of depression.
Comparator	Placebo, or other treatments for depression.
Outcomes	Effectiveness - depressive symptoms, personal functioning, quality of life, any adverse events. Cost-effectiveness.
Study design	Factorial design (followed by RCTs of revised interventions).
Timeframe	Follow-up to at least 24 months after completion of the intervention.
Additional information	Sub-group analysis for older people

Research question

What are the mechanisms of action of effective psychological interventions for acute episodes of depression in adults?

Why this is important

Psychological interventions are complex interventions involving many interacting components and delivery elements. Research is required to identify the mechanisms of action of the effective individual psychological treatments for depression, which would allow for the isolation of the most effective components and the development of more potent, cost-effective and acceptable treatments.

Table 105. Research recommendation rationale

Research question	What are the mechanisms of action of effective psychological interventions for acute episodes of depression in adults?
Importance to 'patients' or the population	Depression is a debilitating and highly prevalent condition in adults. Despite significant investment, the most effective and well-established treatments have only modest effects on depressive symptoms, and more effective treatments for acute depression are therefore required.
Relevance to NICE guidance	A wide variety of psychological interventions are recommended for acute episodes of depression, but improved evidence for the effectiveness of specific components could lead to greater clarity in the recommendations.
Relevance to the NHS	Use of more effective and more cost-effective options may lead to reduced costs for treating people with acute depression.
National priorities	The NHS Five Year Forward plan makes access to effective mental health services a key national priority.
Current evidence base	Very little evidence is available which identifies the mechanisms or components of psychological interventions that contribute most to their effectiveness.
Equality	No equality issues
Feasibility	This research would require a series of experimental studies to identify potential mechanisms associated with current effective treatments for depression which could then be used to inform the development of new treatments. These novel treatments should then be tested in large scale RCTs against current most effective psychological treatments. This would require an extensive programme of research.

Research question	What are the mechanisms of action of effective psychological interventions for acute episodes of depression in adults?
Other comments	None

Table 106. Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (18 years or older) with acute episode of depression.
Intervention	Psychological interventions analysed in terms of into generic therapeutic components (for example therapeutic relationship, rationale; remoralization), therapy structure (for example session duration, frequency), and specific ingredients. The determination of the active components would depend on testing the presence or absence of individual therapeutic elements. The studies will also need to take into account the impact of any moderators of treatment effect including therapist, patient and environment factors.
Comparator	Placebo, or other therapeutic components, structures or specific ingredients.
Outcomes	The research will need to be able to fully characterise the nature and range of depressive symptoms experienced by people and relate these to any proposed underlying neuropsychological mechanisms.
Study design	Factorial design (followed by RCTs of revised interventions).
Timeframe	Follow-up to 24 months after intervention.
Additional information	None

Research question

What is the effectiveness and cost-effectiveness of combination treatment with acupuncture and antidepressants in people with more severe depression in the UK?

Why this is important

There is evidence that combination treatment with acupuncture and antidepressants is effective and cost-effective in more severe depression. However, the evidence for this was based on studies that had been conducted in China, and the committee were aware that Chinese acupuncture may differ from that offered in the the UK. It is therefore important to evaluate the effectiveness of Western-style acupuncture in combination with antidepressants to evaluate if this combination is also effective and cost-effective.

Table 107. Research recommendation rationale

Research question	What is the effectiveness and cost-effectiveness of combination treatment with acupuncture and antidepressants in people with more severe depression in the UK?
Importance to 'patients' or the population	Antidepressants are effective for more severe depression, but people with depression may wish to consider complementary therapies to support improvement in their mood. Acupuncture is not a commissioned service, so only available to people with financial means to pay for them. This may increase health inequalities.

Research question	What is the effectiveness and cost-effectiveness of combination treatment with acupuncture and antidepressants in people with more severe depression in the UK?
Relevance to NICE guidance	The existing evidence for the use of acupuncture is based on Chinese acupuncture which may be different from acupuncture delivered in the Western world, so evidence cannot be extrapolated to UK populations.
Relevance to the NHS	If effective, acupuncture would need to be commissioned as part of the offer for patients with more severe depression.
National priorities	Depression is a common condition, impacting on quality of life of people, including work absence. If acupuncture plus antidepressants is shown to be more effective than antidepressants alone, this may reduce incidence of treatment-resistant depression, poorer patient outcomes and referral to specialist care.
Current evidence base	The evidence-base identified was based on Chinese acupuncture which may be different from acupuncture delivered in the Western world, so evidence cannot be extrapolated to UK populations.
Equality	Acupuncture is not a commissioned service – so only people with financial means can afford to purchase this intervention.
Feasibility	It is likely that acupuncture could be a commissioned service within IAPT or social prescribing services.
Other comments	Acupuncture may be more acceptable than a combination of two antidepressants or other combination of drugs for more severe depression.

Table 108. Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (18 years or older) with acute episode of more severe depression.
Intervention	Western-style acupuncture in combination with antidepressants.
Comparator	Sham acupuncture + placebo.
Outcomes	Critical: • Depression symptomatology (PHQ-9) • Remission • Response

Criterion	Explanation
	• Discontinuation due to side effects (for pharmacological trials) • Discontinuation due to any reason (including side effects). Important: • GAD7 • Quality of life • Personal, social and occupational functioning.
Study design	Randomised 3-arm Controlled Trial, plus nested qualitative study to explore acceptability.
Timeframe	Acupuncture Intervention 6 sessions or 12 sessions (3 arm trial) Follow-up 3, 6 and 12 months, then 24 months after intervention
Additional information	Nested qualitative study vital to explore acceptability of acupuncture and barriers to implementation in routine care.

Research question

What is the incidence and severity of withdrawal symptoms for antidepressant medication?

Why this is important

The committee found relatively little evidence to provide information for people with depression on the withdrawal symptoms for antidepressant medication and to guide recommendations on the best methods for stopping long-term antidepressant treatment.

Table 109. Research recommendation rationale

Research question	What is the incidence and severity of withdrawal symptoms for antidepressant medication?
Why is this needed	
Importance to 'patients' or the population	Antidepressant use is common (more than 10% of adults), and coming off them is difficult for a proportion of people.
Relevance to NICE guidance	More specific guidance is needed on the likely incidence and severity of withdrawal symptoms and how to minimise them.
Relevance to the NHS	The NHS spends around £300M per year on antidepressant prescribing, and consultations for prescribing and managing withdrawal are several times more costly than the prescriptions themselves.
National priorities	All CCGs must, as a minimum, invest in mental health services to meet the Mental Health Investment Standard.

Research question	What is the incidence and severity of withdrawal symptoms for antidepressant medication?
Current evidence base	A 2018 systematic review suggested that withdrawal symptoms on stopping antidepressants were present in more than half of patients, and severe in around half of those suffering them. Davies J, Read J. (2018) A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? (PDF) Addictive Behaviors. 2018 Sep 4. https://doi.org/10.1016/j.addbeh.2018.08.027 However some of the studies included relied on online retrospective self-reporting of symptoms, which would tend to be biased in the direction of greater problems due to the greater salience of the question to people who did recall withdrawal symptoms. A more recent Cochrane review found few studies that examined stopping long-term antidepressants prospectively. A lack of distinction between withdrawal symptoms and relapse in the studies reviewed limited interpretation about the effectiveness and safety of approaches for stopping versus continuing long-term antidepressants. Van Leeuwen E, van Driel ML, Horowitz MA, Kendrick T, Donald M, De Sutter AIM, Robertson L, Christiaens T. Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD013495. DOI:10.1002/14651858.CD013495.pub2. The review recommended future studies should assess (1) the incidence of withdrawal symptoms in patients tapering antidepressants, (2) identification of risk factors to better predict withdrawal symptoms, and (3) the relative advantages of different dose reduction regimens. It has been suggested studies should include tapering SSRI treatment hyperbolically and slowly, in the same way as benzodiazepines are usually withdrawn after a period of prolonged use. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:538-46.

Research question	What is the incidence and severity of withdrawal symptoms for antidepressant medication?
	Ruhe HG, Horikx A, van Avendonk MJP, Woutersen-Koch H. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:561-2.
Equality	NA
Feasibility	No concerns
Other comments	NA

NA: Not applicable

Table 110. Research recommendation modified PICO table

Criterion	Explanation
Population	Adults taking long-term antidepressants for longer than one year for a first episode of depression, or longer than two years for a recurrent episode, who are no longer depressed and wish to come off treatment.
Intervention	Stopping antidepressants slowly (at a rate set according to patient experience) over several months using hyperbolic tapering.
Comparator	Stopping antidepressants in uniform steps of a fixed proportion of the starting dose over 1-2 months.
Outcomes	• Withdrawal symptoms measured using a) the 43-point Discontinuation-Emergent Signs and Symptoms (DESS) checklist, Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry. 1998 Jul 15;44(2):77-87 and b) self-reporting based on self-definition of withdrawal symptoms. • Successful cessation of antidepressants for two months or more. • Relapse of depression measured using a validated measure of depression symptoms.
Study design	RCT
Timeframe	One year
Additional information	Hyperbolically tapering SSRI treatment is done slowly, in the same way as benzodiazepines are usually withdrawn after a period of prolonged use, taking as long as the patient needs to remain free of major withdrawal symptoms. This should be compared with more conventional stepwise reduction, halving the dose and halving it again before stopping altogether. Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:538-46.

Criterion	Explanation
	Ruhe HG, Horikx A, van Avendonk MJP, Woutersen-Koch H. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:561-2.

Appendix M – Network meta-analysis report from the NICE Guidelines Technical Support Unit (TSU)

Network meta-analysis report from the NICE Guidelines TSU for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

TSU, Bristol (Hugo Pedder, Debbi Caldwell and Nicky J Welton)

Acknowledgements: Caitlin Daly, Edna Keeney and Sofia Dias for their contributions to the previous versions of the report for the 2017 and 2018 guideline consultation drafts

Introduction

The purpose of this analysis was to estimate the comparative effectiveness of various interventions for treating a new episode of less severe depression or more severe depression in adults. In total 674 studies were included in these analyses comparing 153 interventions and combinations of interventions.

The outcomes analysed were: discontinuation for any reason; discontinuation due to side effects; remission; response; and standardized mean difference (SMD) on a continuous measurement on various depression scales.

Methods

Network meta-analysis

In order to take all trial information into consideration network meta-analyses (NMA) were conducted. NMA is a generalization of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (Caldwell 2005; Dias 2013; Lu 2004). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments, and, at the same time, allow simultaneous inference on all treatments while respecting randomisation (Caldwell 2005; Lu 2004).

Simultaneous inference on the relative effects of all treatments is possible whenever treatments are part of a single “network of evidence”, that is, every treatment is linked to at least one of the other treatments under assessment. The correlation between the random effects of multi-arm trials (that is, those with more than 2 arms) in the network is taken into account in the analysis (Dias 2013). In a NMA we assume that intervention A is similar (in dose, administration etc.) when it appears in the A vs B and A vs C studies and also that every patient included the network could have been assigned to any of the interventions (Caldwell 2005) – a concept called ‘joint randomisability’ (Salanti 2012).

In the situation where a study compared two treatments that were coded the same way (based on the review protocol), following previous guidelines, we have included them as separate arms. Any differences between the treatments in these arms therefore contributed to between-study SD.

A Bayesian framework is used to estimate all parameters, using Markov Chain Monte Carlo (MCMC) simulation methods implemented in WinBUGS 1.4.3 (Lunn 2000 & 2013). The network reference treatment was selected as the best-connected intervention in the network as this improved model stability and reduced the number of MCMC simulations required for model convergence. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic (Brooks 1998) and was satisfactory by 80,000 simulations for all outcomes (Gelman 1992). A further simulation sample of at least 20,000 iterations post-convergence was obtained on which all reported results were based. Sample WinBUGS code is provided in supplement B5, appendix 1, and full WinBUGS files are included which contain the precise number of simulations for convergence and number of iterations monitored for each outcome.

For binary data, studies with zero or 100% events in all arms were excluded from the analysis because these studies provide no evidence on relative effects (Dias 2011). For studies with zero or 100% events in one arm only, we planned to analyse the data without continuity corrections where computationally possible. Where this was not possible, we used a continuity correction where we added 0.5 to both the number of events and the number of non-events, which has shown to perform well when there is an approximate 1:1 randomisation ratio across intervention arms (Sweeting 2004). For the small number of studies in which there was not an approximate 1:1 randomisation ratio, a continuity correction that was weighted by the reciprocal of the opposite group arm size was used (Sweeting 2004). For studies with >2 arms we extended this weighted continuity correction by using a weighting that was a sum of the sample size in the other treatment arms in the study, and then standardised the weights so that they summed to 1.

Reporting of results

Network diagrams are presented for each population and outcome. The edges (lines) connecting each pair of interventions represent a direct comparison.

Relative intervention effects are reported in the "*Effect size vs Reference*" worksheets of the Excel files included in supplement B6 as posterior median log-odds ratios (log-OR) or standardised mean differences (SMD) and 95% Credible Intervals (CrIs) compared to either Pill placebo (for NMAs of more severe depression) or Treatment As Usual (TAU) (for NMAs of less severe depression). The full list of ORs and SMDs for each intervention and class compared to every other are reported in the "*Treatment Direct Effects*" and "*Class Direct Effects*" worksheets of the Excel files included in supplement B6, respectively.

We also report posterior mean rank of each class, along with the posterior median and 95% CrIs, with the convention that the lower the rank the better the class. These can be found in the "*Ranks*" worksheet of the Excel files included in supplement B6. Only interventions and classes of interest were included in the calculations of the rankings. The interventions that were included in the NMA in order to provide links to the networks but were deemed not of interest by the committee and were therefore excluded from the rankings were:

- No treatment
- Any psychotherapy
- CBT individual (15 sessions or over) + pill placebo
- CBT individual (under 15 sessions) + pill placebo
- Interpersonal psychotherapy individual + pill placebo
- Non-directive/supportive/person-centred counselling + pill placebo
- Computerised-CBT + TAU
- Progressive muscle relaxation individual + pill placebo
- Any SSRI
- Any TCA
- Imipramine

- Any AD

The classes that were included in the NMA in order to provide links to the networks but were deemed not of interest for decision-making by the committee and were therefore excluded from the rankings were

- No treatment
- Any psychotherapy
- Cognitive and cognitive behavioural therapies individual + placebo
- Interpersonal psychotherapy individual + placebo
- Counselling individual + placebo
- Self-help + TAU
- Relaxation individual + placebo
- Any AD

Class models

Classes are groups of interventions which are thought to have similar effects. Class models were used so that strength could be borrowed across treatments in the same class and to reconnect disconnected networks. For all outcomes, random class effect models were used which assume that the effects of treatments in a class are distributed around a common class mean, m_{class}, with a within-class variance, τ^2_{class}. In this way treatment effects are shrunk towards a class mean and can borrow strength from other elements of the class, whilst still estimating distinct effects for each treatment.

The pooled relative treatment effects were assumed to be exchangeable within class:

$$d_{1,k} \sim N\left(m_{D_k}, \tau^2{}_{D_k}\right)$$

where $d_{1,k}$ is the effect of intervention *k* relative to intervention 1, and D_k indicates the class to which treatment *k* belongs.

We note that an error was made in the coding of Interpersonal counselling individual + venlafaxine. This was coded in the dataset as belonging to the Counselling individual + AD class, when it should have been coded as belonging to the Interpersonal psychotherapy (IPT) individual + AD class. This was corrected for SMD outcomes, but for other outcomes the incorrect coding persists. However, this only causes a difference in coding for 13 participants in several of the more severe NMAs. A sensitivity analysis was conducted to assess the impact of this in SMD in more severe depression (see Sensitivity analyses: post-hoc).

For treatments belonging to a class with only one or two treatments in a particular analysis there is insufficient evidence to estimate the within-class variance, however we would still expect there to be heterogeneity between the within class treatment effects. For this reason, the within-class variance was shared with another similar class in the model, where the variability between treatment effects might be expected to be similar. The following rules applied where there was limited information with which to estimate separate class variances (e.g. where classes had only one or two treatments) but variance could be shared with another class for which it could be more reliably estimated. The following variance sharing rules were used when necessary:

- The following classes shared variance with Behavioural therapies individual:
  - Cognitive and cognitive behavioural therapies individual
- The following classes shared variance with Cognitive and cognitive behavioural therapies individual:

  - Behavioural therapies individual
  - Behavioural therapies group
  - Cognitive and cognitive behavioural therapies group
  - Problem solving individual
  - Problem solving group
  - Counselling individual
  - Interpersonal psychotherapy (IPT) individual
  - Psychoeducation group
  - Self-help
  - Self-help with support
  - Long-term psychodynamic psychotherapies individual
  - Short-term psychodynamic psychotherapies individual
  - Short-term psychodynamic psychotherapies group
  - Mindfulness or meditation individual
  - Relaxation individual
  - Cognitive and cognitive behavioural therapies individual + placebo
  - Interpersonal psychotherapy (IPT) individual + placebo
  - Counselling individual + placebo
  - Relaxation individual + placebo
  - Acupuncture
  - Cognitive and cognitive behavioural therapies individual + AD
  - Acupuncture + counselling individual
- The following classes shared variance with Cognitive and cognitive behavioural therapies group:
  - Music therapy group
  - Mindfulness or meditation group
  - Relaxation group
  - Peer support group
  - Yoga group
- The following classes shared variance with Self-help with support:
  - Exercise individual
  - Exercise group
- The following classes shared variance with SSRIs:
  - TCAs
  - SNRIs
- The following classes shared variance with Acupuncture:
  - Sham acupuncture
  - Light therapy
  - Acupuncture + AD
  - Sham acupuncture + AD
  - Light therapy + AD
- The following classes shared variance with Cognitive and cognitive behavioural therapies individual + AD:
  - Self-help + TAU
  - Behavioural therapies individual + AD

  - Cognitive and cognitive behavioural therapies group + AD
  - Problem solving individual + AD
  - Long-term psychodynamic psychotherapy individual + AD
  - Interpersonal psychotherapy (IPT) individual + AD
  - Counselling individual + AD
  - Self-help + AD
  - Short-term psychodynamic psychotherapies individual + AD
  - Psychoeducation group + AD
  - Peer support group + AD
  - Mindfulness or meditation group + AD
  - Relaxation individual + AD
  - Exercise individual + AD
  - Exercise group + AD
  - Yoga group + AD
  - Cognitive and cognitive behavioural therapies individual + exercise group
  - Cognitive and cognitive behavioural therapies group + exercise group
- The following class used the maximum of either the SSRI class variance or the TCA class variance:
  - Any AD
- The following class used the maximum of either the Cognitive and cognitive behavioural therapies individual class variance or the Cognitive and cognitive behavioural therapies group class variance:
  - Any psychotherapy

The following treatments were not allocated to a class, and a single intervention effect estimated (equivalent to a class-effect model with within-class variability ($\tau^2_{D_k} = 0$)):

- Pill placebo
- Attention placebo
- No treatment
- Waitlist
- TAU
- Enhanced TAU
- Mirtazapine
- Trazodone

These assumptions were based on the committee's expert opinion.

If class variances could not be estimated for any psychological/physical/combined therapies (i.e. the absence of class variance information on both Behavioural therapies individual *and* Cognitive and cognitive behavioural therapies individual), then the class variance was shared with the class that had the maximum class variance.

The within-class mean treatment effects were given vague priors m_{class} ~ N(0,100^2) and the within-class standard deviations (SD) were given vague uniform priors τ_{class} ~ Uniform(0,5). In cases where there was evidence that the prior constrained the posterior, the upper limit was extended to 7.

For treatments connected by only a single, small study with zero responders in one of the connecting arms, this sometimes led to convergence issues that could not be resolved

without making additional strong assumptions. In these cases, the treatments were effectively disconnected from the network, meaning that relative effects for them compared to other treatments in the network could not be estimated, and thus are not presented.

Intervention effects are reported for both individual treatments and classes of treatments.

Inconsistency checking

Consistency between the different sources of indirect and direct evidence was explored statistically by comparing the fit of a model assuming consistency with a model which allowed for inconsistency (also known as an unrelated mean effect model) at the treatment-level, whilst still modelling class effects.

Goodness of fit was measured using the posterior mean of the residual deviance, which is a measure of the magnitude of the difference between the observed data and their model predictions (Spiegelhalter 2002). Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points (Spiegelhalter 2002). We also report the Deviance Information Criterion (DIC), which penalises model fit with model complexity (Spiegelhalter 2002). Finally, we report the between studies standard deviation (heterogeneity parameter) to assess the degree of statistical heterogeneity. If the inconsistency model had the smallest posterior mean residual deviance or heterogeneity then this indicated potential inconsistency in the data. In comparing models, differences of ≥5 points for posterior mean residual deviance and DIC were considered meaningful (Spiegelhalter 2002), with lower values being favoured.

Dev-dev plots that plotted individual deviance contributions from both consistency and inconsistency models for each data point are presented for each outcome. Data in which these contributions are substantially different indicate a better fit in either the consistency or inconsistency model and warrant a closer inspection. These points are named and highlighted in the dev-dev plots.

Direct estimates from the unrelated mean effect model are reported in the separate spreadsheets of results for each outcome (supplement B6), and these can be compared to NMA estimates from the consistency models. To identify comparisons for which there was likely to be a discrepancy between direct and indirect estimates, we estimated the indirect evidence contributions by subtracting the direct evidence contributions estimated using the unrelated mean effects model from the NMA estimates estimated using the consistency model, assuming normality of the posterior distributions:

$$d_{ind} = \frac{d_{nma}(w_{dir} + w_{ind}) - w_{dir} d_{dir}}{w_{ind}}$$

Where d_{ind} is the indirect relative effect, d_{nma} is the mixed relative effect estimated from the NMA, d_{dir} is the direct relative effect estimated from the inconsistency model, for a given treatment comparison. w_{nma}, w_{dir} and w_{ind} are the inverse-variance weights, calculated as $\frac{1}{\sigma^2_{nma}}$, $\frac{1}{\sigma^2_{dir}}$ and $\frac{1}{\sigma^2_{ind}}$ for the mixed, direct and indirect effects respectively; σ_{nma} and σ_{dir} are the standard deviations of the posterior distributions for the corresponding relative effects; σ_{ind} is the standard error for the indirect relative effect, calculated as:

$$\sigma_{ind} = \sqrt{\frac{\sigma^2_{nma}\sigma^2_{dir}}{\sigma^2_{dir} - \sigma^2_{nma}}}$$

The difference between direct and indirect estimates can then be estimated, and a Wald test can be used to test whether direct and indirect evidence are in agreement. We acknowledge that the posterior distributions may not be normally distributed, and hence we use this approach as a heuristic to identify comparisons in which direct and indirect evidence are likely to strongly disagree, given the large number of comparisons in many of the networks.

WinBUGS codes for inconsistency models are provided in supplement B5, appendix 6.

SMD analysis: methods

We wished to include as many trials and information as possible in each analysis even when data were reported in different ways. This meant transforming the data in some cases. For the SMD analysis we wanted to conduct a NMA on the mean difference in change from baseline (CFB) (for which standard methods are available, see Dias 2011). The data required for each arm of each study are the mean CFB, the standard deviation in CFB and the total number of individuals in that arm (or the standard error of the mean change from baseline).

However, some studies did not report these data, and instead reported

a) the baseline and endpoint means, standard deviations and number of individuals, for each arm of the study;

b) the number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline;

Studies reporting outcomes a) or b) above also provide information on the mean change from baseline, through the relationship between the underlying continuous scale and the measurements that can be derived from it.

For our analysis, if CFB data were available in a study we used those data. If that study did not report CFB but reported baseline and endpoint data we used the baseline and endpoint data and transformed it to CFB. If a study reported neither CFB nor baseline and endpoint data but did report response, we used the response data and transformed it to CFB. For using intention-to-treat data we required that the number of participants randomised be reported, whilst for per-protocol data we required that the number of completers be reported. If these were not reported consistently for continuous data on CFB, baseline or endpoint, then we preferred to use the number of individuals responding to treatment and derive the continuous results from this.

Notation

To transform the data we assumed that n_{ik} individuals are randomised to each arm k (k>1) of study i=1,…,M, on which the following outcomes are recorded for individual j=1,…,n_{ik}:

x_{jik} - the score at baseline for individual j in arm k of trial i, on a given continuous scale;

y_{jik} - the score at follow-up for individual j in arm k of trial i, on a given continuous scale;

c_{jik} - the change from baseline for individual j in arm k of trial i, on a given continuous scale, where $c_{jik} = y_{jik} - x_{jik}$;

R_{jik} - response status at endpoint for individual j in arm k of trial i, defined as **at least a q_i*100% reduction** of the endpoint measurement on a given continuous scale, compared to baseline, i.e.

$$R_{jik} = \begin{cases} 1 & \text{if } y_{jik} - x_{jik} \leq -q_i x_{jik} \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

Note that different studies may have used a different cut-off *q* (although they would be expected to be the same for all arms of a study), and these are therefore indexed by study.

Reported outcomes

Studies may report all or some of the following observed outcomes

$m_{X,ik}$ - the observed mean at baseline in arm *k* of trial *i*, on a given continuous scale;

$sd_{X,ik}$ - the observed standard deviation at baseline in arm *k* of trial *i*, on a given continuous scale;

$m_{Y,ik}$ - the observed mean at endpoint in arm *k* of trial *i*, on a given continuous scale;

$sd_{Y,ik}$ - the observed standard deviation at endpoint in arm *k* of trial *i*, on a given continuous scale;

$m_{C,ik}$ - the observed mean change from baseline in arm *k* of trial *i*, on a given continuous scale;

$sd_{C,ik}$ - the observed standard deviation in change from baseline in arm *k* of trial *i*, on a given continuous scale;

ρ_{ik} - the observed correlation between baseline and endpoint scores measured on the same individual in arm *k* of trial *i*. (Although this is rarely reported directly, it can be calculated when the means and standard deviations at baseline, endpoint and from the CFB are provided);

$r_{resp,ik}$ - the number of individuals achieving response in arm *k* of trial *i*, with response defined in equation (1).

Relationship between different outcomes

We assume that for each patient the baseline and endpoint measurements are sampled from a bivariate Normal distribution. Thus for all patients in arm *k* of trial *i*, we assume that their baseline, X_{ik}, and endpoint measurements Y_{ik}, are independent and identically distributed as

$$\begin{pmatrix} X_{ik} \\ Y_{ik} \end{pmatrix} \sim \mathrm{N}_2\left(\begin{pmatrix} \mu_{X,ik} \\ \mu_{Y,ik} \end{pmatrix}, \begin{pmatrix} \sigma^2_{X,ik} & \rho_{ik}\sigma_{X,ik}\sigma_{Y,ik} \\ \rho_{ik}\sigma_{X,ik}\sigma_{Y,ik} & \sigma^2_{Y,ik} \end{pmatrix}\right) \quad (2)$$

with $\mu_{X,ik}$ and $\mu_{Y,ik}$ representing the means and $\sigma^2_{X,ik}$ and $\sigma^2_{Y,ik}$ the variances at baseline and endpoint for individuals in arm *k* of trial *i*, respectively, and ρ_{ik} being the within arm and study correlation between baseline and endpoint measurements on the same individuals.

We define the mean change from baseline in arm *k* of trial *i* as $\theta_{ik} = \mu_{Y,ik} - \mu_{X,ik}$ as the parameter of interest.

NMA model for continuous outcomes

With continuous outcome data, meta-analysis is usually based on the sample means, with standard errors assumed known. Here we are interested in modelling the mean changes from baseline, which are assumed to be approximately normally distributed, with likelihood

$$m_{C,ik} \sim N\left(\theta_{ik}, se^2_{C,ik}\right)$$

The parameter of interest is the mean, θ_{ik}, of this distribution. For a random effects model we write

$$\theta_{ik} = \gamma_i + \delta_{ik} \quad (3)$$

where γ_i are the trial-specific effects of the treatment in arm 1 of trial *i*, treated as unrelated nuisance parameters, and the δ_{ik} are the trial-specific treatment effects of the treatment in arm *k* relative to the treatment in arm 1 in that trial, where $\delta_{i1} = 0$. The trial-specific random effects δ_{ik}, represent the mean differences between the change from baseline for the treatment in arm *k* and the treatment in arm 1 of trial *i* and, in a random effects model,

$$\delta_{ik} \sim \text{Normal}(d_{t_{i1},t_{ik}}, \tau^2_{study}) \quad (4)$$

where τ^2_{study} denotes the between-study heterogeneity, assumed common to all treatment comparisons and $d_{t_{i1}t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$ are the pooled mean differences, defined by the consistency equations ($d_{11} = 0$). The fixed effect model is obtained by replacing equation (3) with $\theta_{ik} = \gamma_i + d_{1,t_{ik}} - d_{1,t_{i1}}$. Where studies with more than 2 arms are present, a correlation is induced in the trial specific effects δ_{ik} so equation (4) is replaced by a multivariate normal distribution with correlation equal to 0.5 (Dias 2011; Higgins 1996).

Likelihood and link functions for studies reporting other outcomes

- Studies reporting mean and variance at endpoint

From the joint bivariate normal distribution in equation (2) we know that

$$\left(Y_{ik} - X_{ik}\right) \sim N\left(\theta_{ik}, \sigma^2_{X,ik} + \sigma^2_{Y,ik} - 2\rho_{ik}\sigma_{X,ik}\sigma_{Y,ik}\right) \quad (5)$$

Therefore, studies not reporting change from baseline but reporting the mean and variance at baseline and endpoint also provide information on the parameter of interest θ_{ik}, the mean change from baseline.

For these studies we can calculate the mean change from baseline as $m_{C,ik} = m_{Y,ik} - m_{X,ik}$. Using equation (5), the likelihood can be written as

$$m_{C,ik} \sim N\left(\theta_{ik}, se^2_{X,ik} + se^2_{Y,ik} - 2\rho_{ik}se_{X,ik}se_{Y,ik}\right)$$

Provided the standard errors at baseline and endpoint can be obtained and that we have information on the within-study correlation, the remaining model is given in equations (3) and (4) can be used to pool the mean differences in change from baseline.

- Studies reporting number of responders

Using equation (1), the probability of response for individuals in arm *k* of trial *i* is defined as

$$R_{ik} = \Pr(Y_{ik} - X_{ik} \leq -qX_{ik}) \tag{6}$$

Conditioning on the baseline value X_{ik} we have

$$Y_{ik} \mid X_{ik} \sim N\left(\mu_{X,ik}(1-\rho_{ik}) + \theta_{ik} + \rho_{ik}X_{jik}, (1-\rho_{ik}^2)\sigma_{X,ik}^2\right) \tag{7}$$

thus,

$$\begin{aligned} R_{ik} \mid X_{ik} &= \Pr_{Y|X}\left(Y_{ik} < (1-q)X_{ik}\right) \\ &= \Phi\left(aX_{ik} + b\right) \end{aligned} \tag{8}$$

with

$$a = \frac{1-q-\rho_{ik}}{\sigma_{X,ik}\sqrt{1-\rho_{ik}^2}}\ ,\ b = -\frac{\mu_{X,ik}(1-\rho_{ik}) + \theta_{ik}}{\sigma_{X,ik}\sqrt{1-\rho_{ik}^2}}$$

Therefore the unconditional probability of response in arm *k* of trial *i* is

$$R_{ik} = E_{X_{ik}}\left[\Phi\left(aX_{ik} + b\right)\right] \tag{9}$$

It can be shown that

$$E_X\left[\Phi\left(aX + b\right)\right] = \Phi\left(\frac{aE(X) + b}{\sqrt{1 + a^2 Var(X)}}\right) \tag{10}$$

thus the probability of response for individuals in arm *k* of trial *i* can be written as

$$R_{ik} = \Phi\left(\frac{-(q\mu_{X,ik} + \theta_{ik})}{\sigma_{X,ik}\sqrt{1 + (1-q)(1-q-2\rho_{ik})}}\right) \tag{11}$$

Therefore, studies not reporting the change from baseline or endpoint measures, but providing information on the probability of response, also provide information on the parameter of interest, the mean change from baseline θ_{ik}.

These studies have a binomial likelihood

$$r_{resp,ik} \sim \text{Binomial}(R_{ik}, n_{ik})$$

Provided the baseline mean and standard deviation for each study are reported and that we also have information on the correlation between baseline and endpoint scores in each arm of each study, we can replace these as if they are known into equation (11) and then use equations (3) and (4), as before.

Prior distributions and computation

In this case non-informative prior distributions are chosen for the pooled treatment effects, relative to treatment 1, d_{1k}, k=2,…,nt , where nt is the number of treatments in the network

$$d_{1k} \sim \text{Normal}(0, 100^2) \quad (12)$$

and a Uniform prior between 0 and 5 is chosen for the between-study heterogeneity, which is thought to be sufficiently wide to capture the variability in difference in mean change from baseline across trials making the same comparisons.

An informative prior distribution for the within class standard deviation is given as detailed under '*Class models*'.

Analysis on the SMD scale

In this case, studies also used different underlying continuous scales on which they report the means or the number of responders. As the methods noted above are study and arm specific, they apply regardless of which scale was used in that trial, although care needs to be taken to ensure that the pre-specified cut-offs *q* and *h* are appropriate for the scale used in a particular study.

Pooling of the difference in means across different scales is not appropriate. A common approach is to use the SMD, where the mean difference is divided by a standardising constant, which can be the population standard deviation for each scale (if known), or its estimate, s_i. We use the baseline SD as the standardising constant because it is not influenced by treatment, so better reflects the SD of the outcome scale in the RCT population (Daly 2021).

The standardising constant can be adjusted in different ways (Cooper 2009). We use Cohen's d (Cohen 1969), but the analysis using another standardising constant can be done following the same principles.

The SMD for arm *k* of study *i* compared to arm 1 of study i, λ_{ik} , is given as

$$\lambda_{ik} = \frac{m_{ik} - m_{i1}}{s_i} \quad (13)$$

where s_i in a two arm study is given as

$$s_i = \sqrt{\frac{(n_{i1}-1)sd^2_{i1} + (n_{i2}-1)sd^2_{i2}}{n_{i1} + n_{i2} - 2}} \quad (14)$$

and in a three arm study is given as

$$s_i = \sqrt{\frac{(n_{i1}-1)sd^2_{i1} + (n_{i2}-1)sd^2_{i2} + (n_{i3}-1)sd^2_{i3}}{n_{i1} + n_{i2} + n_{i3} - 3}} \quad (15)$$

The likelihood for each study reporting the various outcomes are as before, but the parameter of interest is now the SMD λ_{ik} . Thus the model is defined as

$$\lambda_{ik} = \gamma_i + \delta_{ik} \quad (16)$$

This model is linked to the mean change from baseline through the following relationship

$$\theta_{ik} = \lambda_{ik} s_i \quad (17)$$

Prior distributions can be defined as before.

Response analysis: methods

The economic model is driven by the probabilities of response on each treatment which are informed both by studies reporting response and studies reporting continuous measures. Again we wanted to include as much data as possible in the analysis. For studies not reporting response we transformed the continuous data first to the SMD scale and then to response. The data required for each arm of each study are the number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline;

However, some studies did not report these data, and instead reported

a) the mean CFB, the standard deviation in CFB and the total number of individuals in that arm (or the standard error of the mean change from baseline);

b) the baseline and endpoint means, standard deviations and number of individuals, for each arm of the study.

Studies reporting outcomes a) or b) above also provide information on the probability of response through the relationship between the underlying continuous scale and the measurements that can be derived from it.

For this analysis, if response data were available in a study we used those data. If that study did not report response but reported CFB we used the CFB data and transformed these to response. If a study reported neither response nor CFB but did report baseline and endpoint data, we used the baseline and endpoint data and transformed these to response.

Continuous SMD data were converted to LOR following the approach recommended by the Cochrane collaboration (Higgins 2011). For trials reporting response the following model was used:

$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})$$

where r_{jk} is the number of individuals achieving response in arm k of trial j, n_{jk} is the total number of individuals in arm k of trial j, and p_{jk} is the probability of response in arm *k* of trial *j*. These probabilities are modelled on the log-odds scale as:

$$\text{logit}(p_{ik}) = \alpha_i + \eta_{ik}$$

where η_{ik} represents the relative treatment effect of the treatment in arm *k* compared with the treatment in arm 1 in trial *i*, on the log-odds ratio (LOR) scale and $\eta_{i1} = 0$. Thus $\eta_{ik} > 0$ favours the treatment in arm *k* and $\eta_{ik} < 0$ favours the treatment in arm 1.

The LOR of response can be related to a notional SMD for response using the formula (Chinn 2000):

$$LOR_{\text{Re}sponse} = \frac{\pi}{\sqrt{3}} SMD_{\text{Re}sponse} \quad (18)$$

noting the change in sign to retain the interpretation of a positive LOR favouring treatment *k*.

The LOR was obtained by transforming the treatment effect from the SMD scale using equation (18). So, the treatment effect on response is informed by the treatment effect in studies on the pooled scale of symptoms as:

$$\eta_{ik} = \left(-\frac{\pi}{\sqrt{3}} \delta_{ik} \right)$$

Standard NMA random and fixed effects model can used to pool η, as described in section '*SMD analysis: methods'* under subsection '*NMA model for continuous outcomes*'. Prior distributions can also be defined as before.

Sample WinBUGS code for both the SMD and response analyses is provided in supplement B5, appendix 1.

Information on within-study correlation and standard deviation at follow-up

To apply the methods described in sub-sections of '*Likelihood and link functions for studies reporting other outcomes*' within section '*SMD analysis: methods*' we needed information on a) the correlation between baseline and endpoint scores and b) the relationship between standard deviations (SDs) at baseline and endpoint.

For a) we identified 35 studies in our dataset that provided information on mean and SD at baseline, mean and SD at endpoint and the mean and SD of change from baseline (supplement B5, appendix 2). The correlations had a median of 0.31 (Inter-Quartile Range: 0.18-0.47), and this value was used for subsequent calculations. In the 2017 and 2018 guideline consultation drafts, a sensitivity analysis exploring different values for the correlation was performed (0.5 or 0.3), which was found to have very little effect. However in that version, unlike in our current analysis, there were also insufficient data points to empirically inform the correlation.

For b) we plotted the SDs at baseline and endpoint from every study that reported both by group of intervention and population (Figure 68 and Figure 69). The blue line on these plots is the regression line with 95% confidence interval and the red line is the line of equality where y=x. The regression equation is also shown. We used the regression equation to predict SD at endpoint from SD at baseline in studies where SD at endpoint was not reported using the regression equations given. No sensitivity analysis was conducted on this, but 2017 and 2018 guideline consultation drafts explored this and found that results were very similar between SDs predicted using a regression equation, and SDs predicted assuming that baseline and endpont were equal.

Figure 68. Plot of SDs at baseline and endpoint – More severe depression.

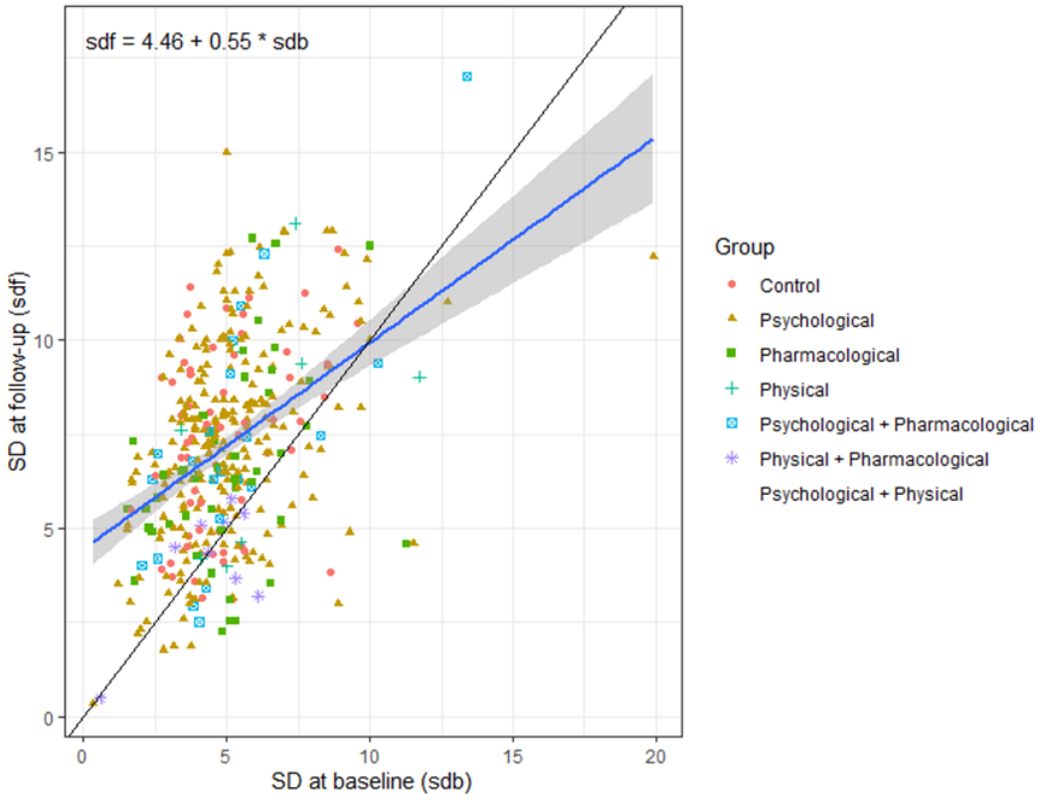
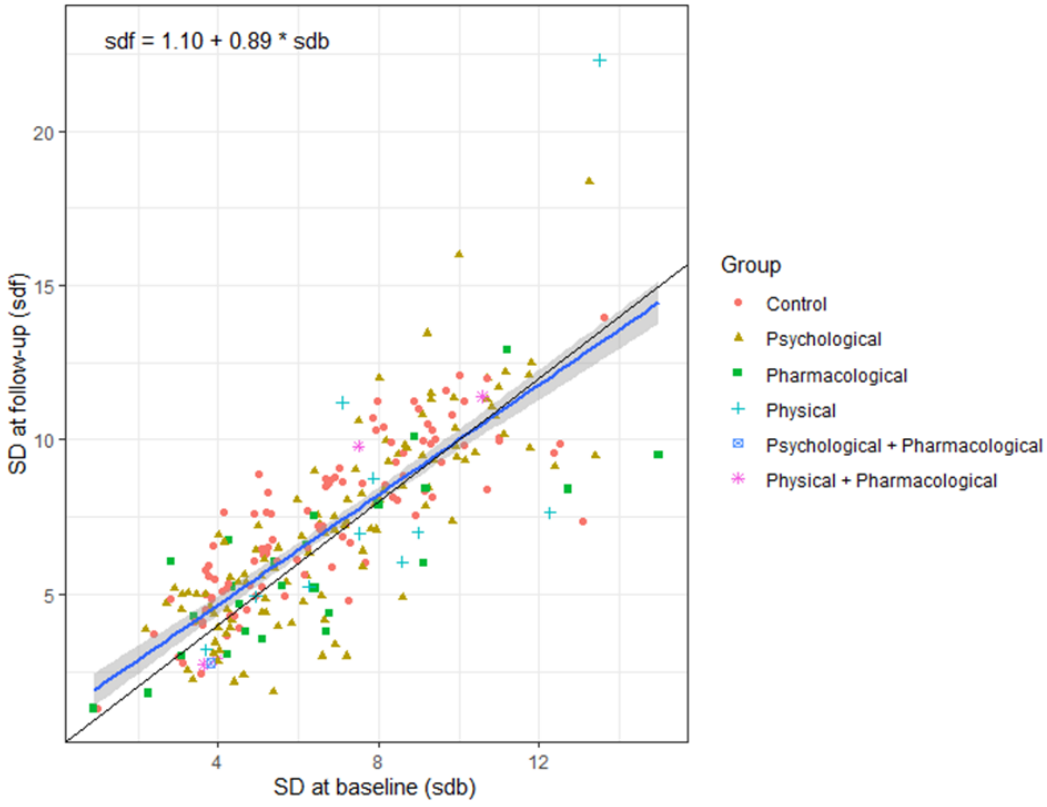


Figure 69. Plot of SDs at baseline and endpoint – Less severe depression.



Pre-specified sensitivity analyses

In selected outcomes (discontinuation due to any reason, response in completers, and Standardised Mean Differences) in both less severe and more severe depression, we evaluated the potential for small study bias using the methods reported by Dias 2010. Adjusting for small study effects captures a range of potential biases that are associated with smaller studies, including, but not restricted to, publication bias. In the absence of sufficient information to explore other risk of bias domains, the best proxy available is to explore the effect of study size, which is often associated with risk of bias indicators. The analysis of small study effects has the benefit that all studies can be included in the analyses simultaneously, thus increasing power to detect any effect.

Bias was assumed in comparisons of active interventions vs inactive control, and no bias was assumed between inactive control comparisons, as well as between active intervention comparisons. Additionally, in comparisons where counselling was the control intervention, bias against counselling was assumed. The bias was assumed to be of the same magnitude across all potentially biased comparisons.

The bias model acts to change the relative treatment effects of the treatment in arm *k* compared to the treatment in arm 1, for each study *i* on the outcome scale being modelled (SMD or logOR). This applies to the relative effects estimated from all included studies, whether the data are reported as change from baseline in measures of depression, depression measured at endpoint or as the number of responders to treatment. The only change required to incorporate the bias adjustment is to change equation (3) to

$$\theta_{ik} = \gamma_i + \delta_{ik} + \left(\beta_{ik} \times V_{ik}\right)$$

where $\delta_{i1} = \beta_{i1} = V_{i1} = 0$, V_{ik} is the variance of the relative effect measure calculated for arm *k* of study *i* compared to arm 1, and β_{ik} represents the bias coefficient for the comparison of the treatment in arm *k* to the treatment in arm 1 of study *i* which is assumed to follow a Normal distribution

$$\beta_{ik} \sim \text{Normal}(B, \kappa^2_{SMD})$$

where *B*=*b* if the treatment in arm 1 of trial *i* is a control and the treatment in arm *k* is not and *B*=0 if the comparison of treatment 1 to treatment *k* is active vs active or control vs control.

Bias-adjusted models were compared to random effects consistency models using DIC. If the bias-adjusted model had a DIC that was lower by ≥5 then results from this were reported over the unadjusted model (Spiegelhalter 2002).

WinBUGS codes for bias-adjusted models are provided in supplement B5, appendix 6.

For Standardised Mean Differences, a non-pharmacological subgroup of the overall dataset was analysed separately as a further sensitivity analysis. This excluded any studies that investigated pharmacological interventions in any arm.

Results for adults with a new episode of less severe depression

Outcome: Discontinuation (for any reason)

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients randomized. After excluding trials with zero events in all arms or with the number events equal to the denominator in all arms, 120 trials of 75 interventions and 34 classes were included for this outcome (Table 111,

Figure 70, Figure 71). A continuity correction was applied to data in 7 studies containing at least one zero cell to stabilize the results.

Lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, as well as minimal improvement in the prediction of data in individual studies by the inconsistency model, suggested that there was no evidence of inconsistency (supplement B5, Table 3.1 in appendix 3; Figure 72). The between-study heterogeneity was very similar in consistency and inconsistency models.

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling treatments was estimated to be 0.14 (95%CrI -0.26, 0.58). Although the between study heterogeneity was slightly reduced (supplement B5, Table 3.1 in appendix 3; Figure 72), the DIC remained the same as in the base-case consistency model. Further details are given in 'Sensitivity Analyses' section). Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ("*Depression NMA less severe DISCONany bias-adjusted*.xlsx" and *"Depression NMA less severe DISCONany base-case.xlsx"*, respectively).

Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.53\ (95\%\ \text{CrI}\ 0.38\ \text{to}\ 0.70)$). Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.1 & 4.2 in appendix 4).

Table 111. Interventions, classes and number of patients randomised (N). Discontinuation (for any reason) analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	3785	Waitlist	1	3785	
2	Pill placebo	621	Placebo	2	621	
3	Attention placebo	795	Attention placebo	3	795	
4	No treatment	1713	No treatment	4	1713	
5	TAU	1005	TAU	5	1005	
6	Enhanced TAU	96	Enhanced TAU	6	96	
7	Behavioural activation (BA) individual	153	Behavioural therapies individual	7	153	1
8	Behavioural activation (BA) group	107	Behavioural therapies group	8	373	1
9	Coping with Depression course (group)	266				
10	CBT individual (15 sessions or over)	90	Cognitive and cognitive behavioural therapies individual	9	663	1
11	CBT individual (under 15 sessions)	402				
12	Third-wave cognitive therapy individual	171				
13	CBT group (15 sessions or over)	47	Cognitive and cognitive behavioural therapies group	10	483	2
14	CBT group (under 15 sessions)	283				

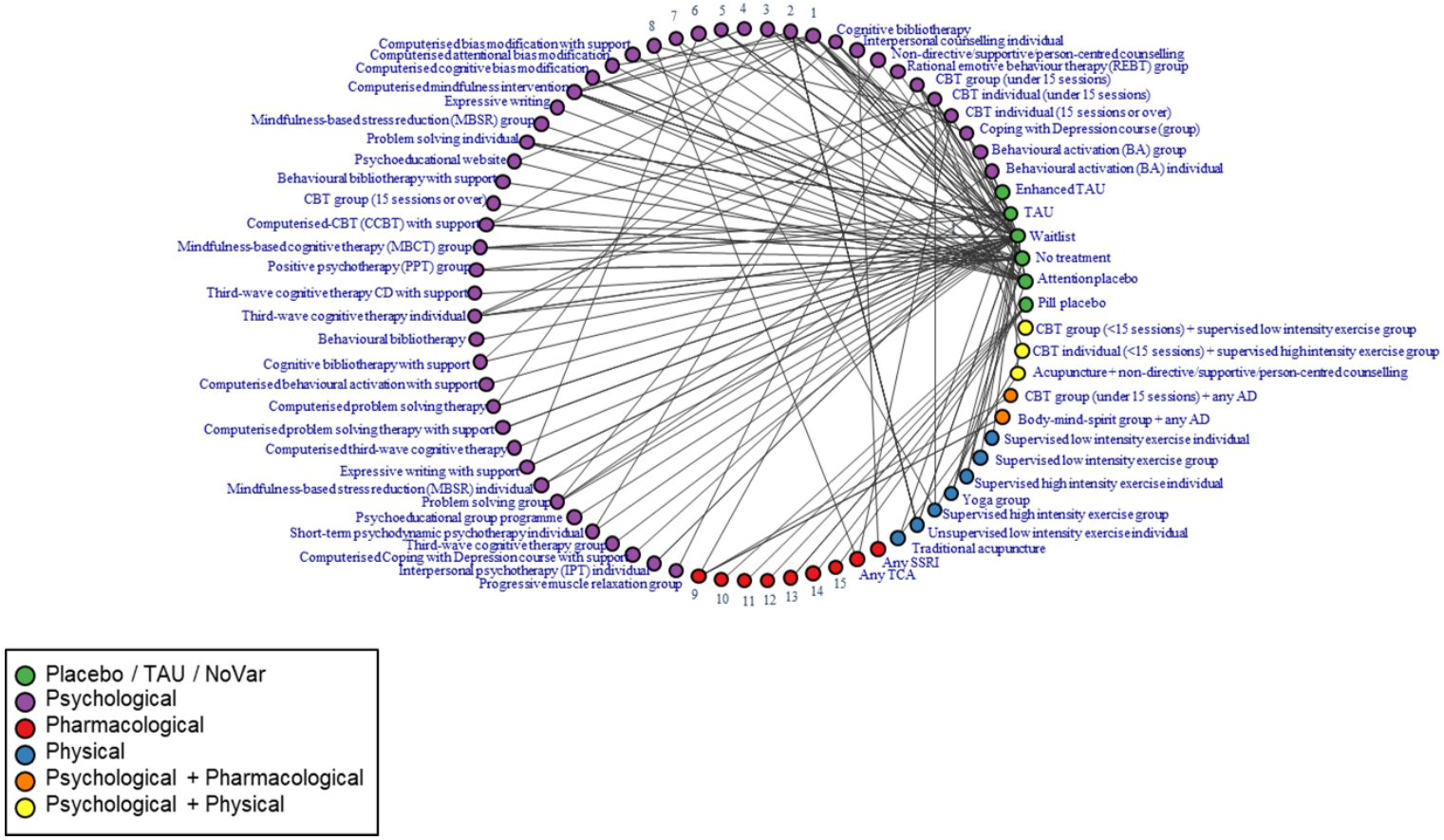
15	Positive psychotherapy (PPT) group	89				
16	Rational emotive behaviour therapy (REBT) group	15				
17	Third-wave cognitive therapy group	49				
18	Problem solving individual	159	Problem solving individual	11	159	1
19	Problem solving group	168	Problem solving group	12	168	1
20	Non-directive/supportive/person-centred counselling	125	Counselling individual	13	125	1
21	Interpersonal counselling individual	27	Interpersonal psychotherapy (IPT) individual	14	135	1
22	Interpersonal psychotherapy (IPT) individual	108				
23	Psychoeducational group programme	23	Psychoeducation group	15	23	1
24	Behavioural bibliotherapy	13	Self-help	16	5733	3
25	Cognitive bibliotherapy	427				
26	Computerised-CBT (CCBT)	3173				
27	Computerised attentional bias modification	154				
28	Computerised behavioural activation	159				
29	Computerised cognitive bias modification	76				
30	Computerised Coping with Depression course	292				
31	Computerised expressive writing	44				
32	Computerised mindfulness intervention	645				
33	Computerised positive psychological intervention	440				
34	Computerised problem solving therapy	101				
35	Computerised third-wave cognitive therapy	31				
36	Expressive writing	13				
37	Psychoeducational website	165				
38	Behavioural bibliotherapy with support	67	Self-help with support	17	1391	4
39	Cognitive bias modification with support	32				
40	Cognitive bibliotherapy with support	125				
41	Computerised-CBT (CCBT) with support	428				
42	Computerised behavioural activation with support	41				
43	Computerised Coping with Depression course with support	36				

44	Computerised problem solving therapy with support	124				
45	Computerised third-wave cognitive therapy with support	82				
46	Expressive writing with support	125				
47	Third-wave cognitive therapy CD with support	331				
48	Short-term psychodynamic psychotherapy individual	53	Short-term psychodynamic psychotherapies individual	18	53	1
49	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	19	20	1
50	Mindfulness-based cognitive therapy (MBCT) group	167	Mindfulness or meditation group	20	375	5
51	Mindfulness-based stress reduction (MBSR) group	70				
52	Mindfulness meditation group	138				
53	Progressive muscle relaxation individual	15	Relaxation individual	21	15	1
54	Progressive muscle relaxation group	63	Relaxation group	22	63	2
55	Any SSRI	28	SSRIs	23	462	6
56	Citalopram	27				
57	Fluoxetine	81				
58	Sertraline	326				
59	Amitriptyline	90	TCAs	24	208	7
60	Any TCA	13				
61	Imipramine	73				
62	Lofepramine	32				
63	Any AD	107	Any AD	25	107	8
64	Traditional acupuncture	40	Acupuncture	26	40	1
65	Supervised high intensity exercise individual	39	Exercise individual	27	235	9
66	Supervised low intensity exercise individual	61				
67	Unsupervised low intensity exercise individual	135				
68	Supervised high intensity exercise group	121	Exercise group	28	181	4
69	Supervised low intensity exercise group	60				
70	Yoga group	78	Yoga group	29	78	2
71	CBT group (under 15 sessions) + any AD	35	Cognitive and cognitive behavioural therapies group + AD	30	35	1
72	Body-mind-spirit group + any AD	44	Mindfulness or meditation group + AD	31	44	1
73	Traditional acupuncture + non-directive/supportive/person-centred counselling	40	Acupuncture + counselling individual	32	40	1

74	CBT individual (under 15 sessions) + supervised high intensity exercise group	21	Cognitive and cognitive behavioural therapies individual + exercise group	33	21	1
75	CBT group (under 15 sessions) + supervised low intensity exercise group	35	Cognitive and cognitive behavioural therapies group + exercise group	34	35	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 70. Network diagram of interventions. Discontinuation (for any reason).



1 Computerised CBT (CCBT), 2 Computerised behavioural activation, 3 Computerised Coping with Depression course, 4 Computerised expressive writing, 5 Computerise positive psychological intervention, 6 Computerised third wave cognitive therapy with support, 7 Mindfulness meditation group, 8 Progressive muscle relaxation individual, 9 Any AD, 10 Amitryptyline, 11 Citalopram, 12 Fluoxetine, 13 Imipramine, 14 Lofepramine, 15 Sertraline.
Without the use of a class model Pill placebo, Interpersonal counselling individual, Amitriptyline, Any SSRI, Citalopram, Fluoxetine, Imipramine, Lofepramine and Sertraline would be disconnected from the rest of the network.

Figure 71. Network diagram of classes. Discontinuation (for any reason).

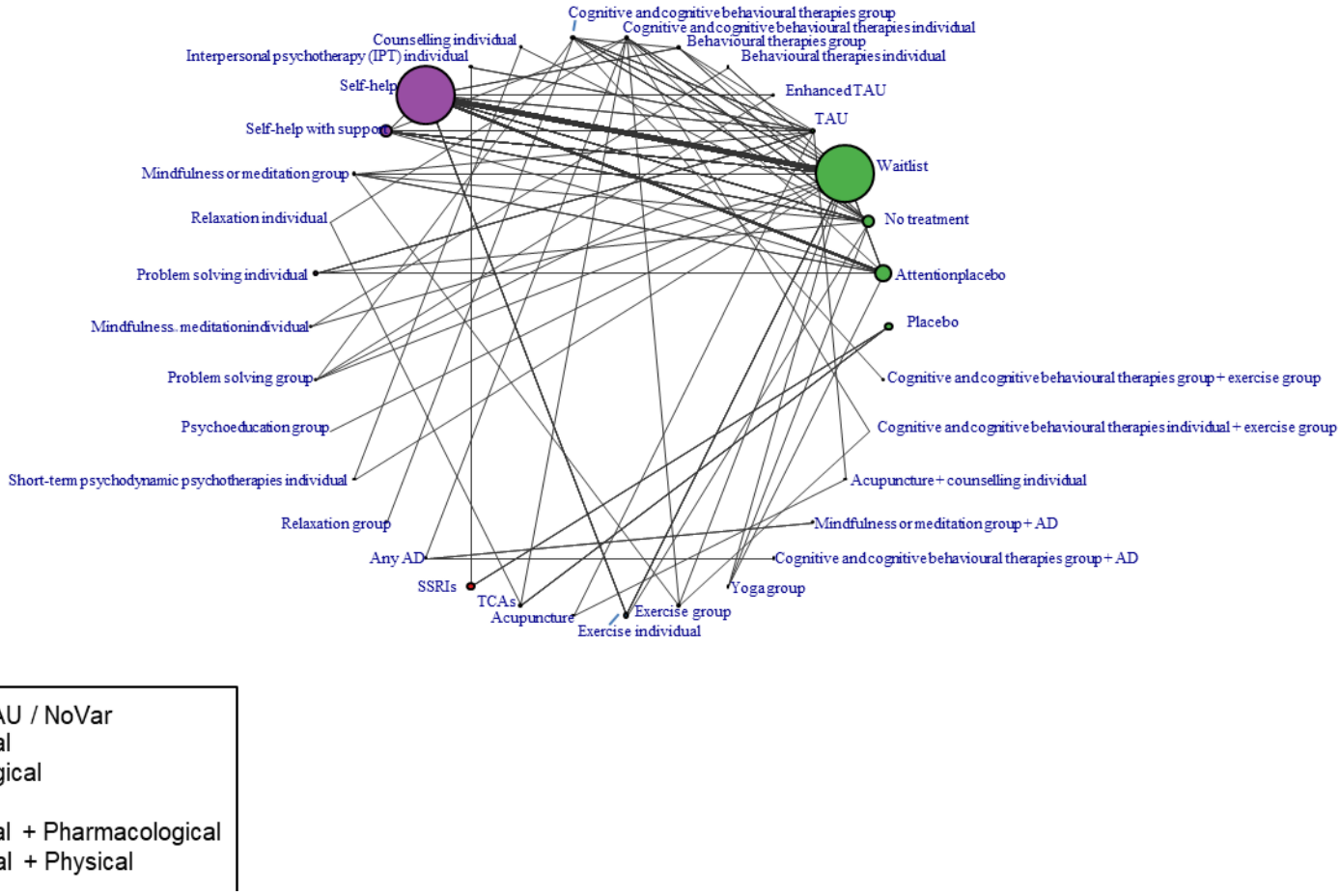
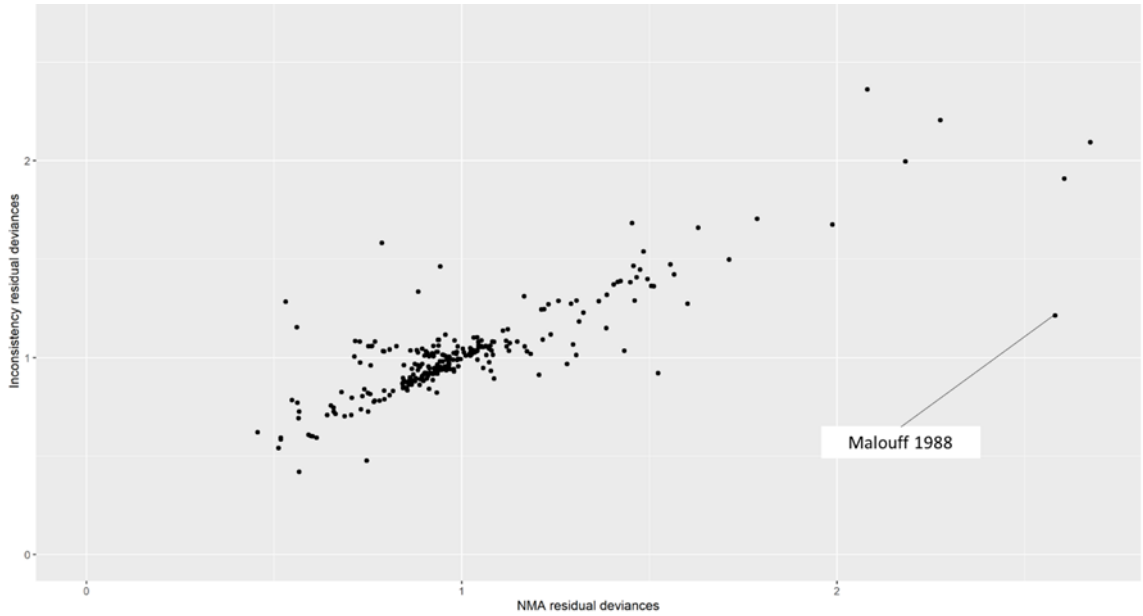


Figure 72. Deviance plot. Discontinuation (for any reason).



There is evidence of only two interventions having a decreased odds of discontinuation compared to TAU (supplement B5, Figure 4.1 in appendix 4):

- No treatment
- Waitlist

There is no clear evidence of any intervention having an increased odds of discontinuation compared to TAU, nor is there evidence of any classes of interventions having a decreased or increased odds of discontinuation compared to TAU (supplement B5, Figures 4.1 & 4.2 in appendix 4). For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

The highest ranked class is Psychoeducation group with a posterior median rank of 4th (95% CrI 1st to 25th) (Table 112). The lowest ranked classes are TCAs, Problem solving group and Enhanced TAU (Table 112). We note however the wide credible intervals in the all ranks, reflecting the uncertainty in which class or treatment is best.

Table 112. Posterior mean and median rank and 95% credible intervals by class. Discontinuation (for any reason).

Class	Posterior mean rank	Posterior median rank (95% CrI)
Psychoeducation group	6.1	4 (1, 25)
Short-term psychodynamic psychotherapies individual	8.2	6 (1, 27)
Waitlist	9.9	10 (5, 16)
Cognitive and cognitive behavioural therapies individual	9.9	9 (3, 23)
Counselling individual	10.0	8 (1, 28)
Cognitive and cognitive behavioural therapies individual + exercise group	11.1	9 (1, 30)
Relaxation group	11.4	7 (1, 32)
Behavioural therapies individual	11.4	8 (1, 31)
Yoga group	12.6	10 (1, 32)

Acupuncture + counselling individual	13.2	11 (1, 31)
Mindfulness or meditation group	13.5	13 (2, 30)
Attention placebo	15.2	15 (9, 23)
Acupuncture	15.7	15 (2, 31)
Mindfulness or meditation individual	15.8	15 (1, 32)
Exercise individual	15.8	15 (2, 31)
Cognitive and cognitive behavioural therapies group + AD	16.6	16 (1, 32)
Mindfulness or meditation group + AD	16.8	17 (1, 32)
TAU	18.1	18 (10, 26)
Exercise group	18.2	18 (6, 29)
Cognitive and cognitive behavioural therapies group	18.3	19 (4, 31)
Self-help	19.3	19 (13, 26)
SSRIs	19.8	22 (2, 32)
Self-help with support	20.2	20 (12, 28)
Problem solving individual	20.7	22 (4, 31)
Placebo	20.8	24 (2, 32)
Behavioural therapies group	20.8	22 (7, 31)
Cognitive and cognitive behavioural therapies group + exercise group	21.6	24 (3, 32)
Interpersonal psychotherapy (IPT) individual	21.8	23 (6, 32)
Relaxation individual	21.9	26 (2, 32)
TCAs	23.2	27 (3, 32)
Problem solving group	24.7	27 (6, 32)
Enhanced TAU	25.5	27 (13, 32)

Outcome: Discontinuation due to side effects

There were insufficient studies and interventions available to be able to fit a NMA with random class effects. Therefore, a simpler fixed class model was fitted, in which all interventions within a class were assumed to have the same effect. As this outcome informed the guideline economic analysis, details of this analysis are provided in appendix J, under '*Relative effects on efficacy, acceptability and tolerability of treatments for a new depressive episode and methods of evidence synthesis*'. Results are also summarised in supplement B5, Figures 4.3 & 4.4 in appendix 4.

Outcome: Remission in completers

This remission analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who completed treatment. After excluding trials which did not report remission in completers, trials with zero events in all arms, trials with the number events equal to the denominator in all arms, and 2 trials that were disconnected from the network, 27 trials of 27 interventions and 17 classes were included for this outcome (Table 113, Figure 73, Figure 74). A continuity correction was applied to data in 2 studies containing at least one zero cell to stabilize the results.

Lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, as well as minimal improvement in the prediction of data in individual studies by the inconsistency model, suggested that there was no evidence of inconsistency (supplement B5, Table 3.3 in appendix 3; Figure 75). The between-study heterogeneity was very similar in consistency and inconsistency models. Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} =$

0.53 $(95\%$ CrI 0.38 to $0.70))$. Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.5 & 4.6 in appendix 4).

Posterior mean residual deviances were the same in the NMA random effects consistency model and the inconsistency model, and DIC was slightly lower. In addition to minimal improvement in the prediction of data in individual studies by the inconsistency model, this suggested that there was no evidence of inconsistency (supplement B5, Table 3.3 in appendix 3; Figure 75). However, both models poorly predicted data from two studies (Yang 2015, Rosso 2017), both of which investigated No treatment compared to an intervention from the Self-help class. The between-study heterogeneity was very similar in consistency and inconsistency models. Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.35$ $(95\%$ CrI 0.02 to $0.89)$). Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.5 & 4.6 in appendix 4).

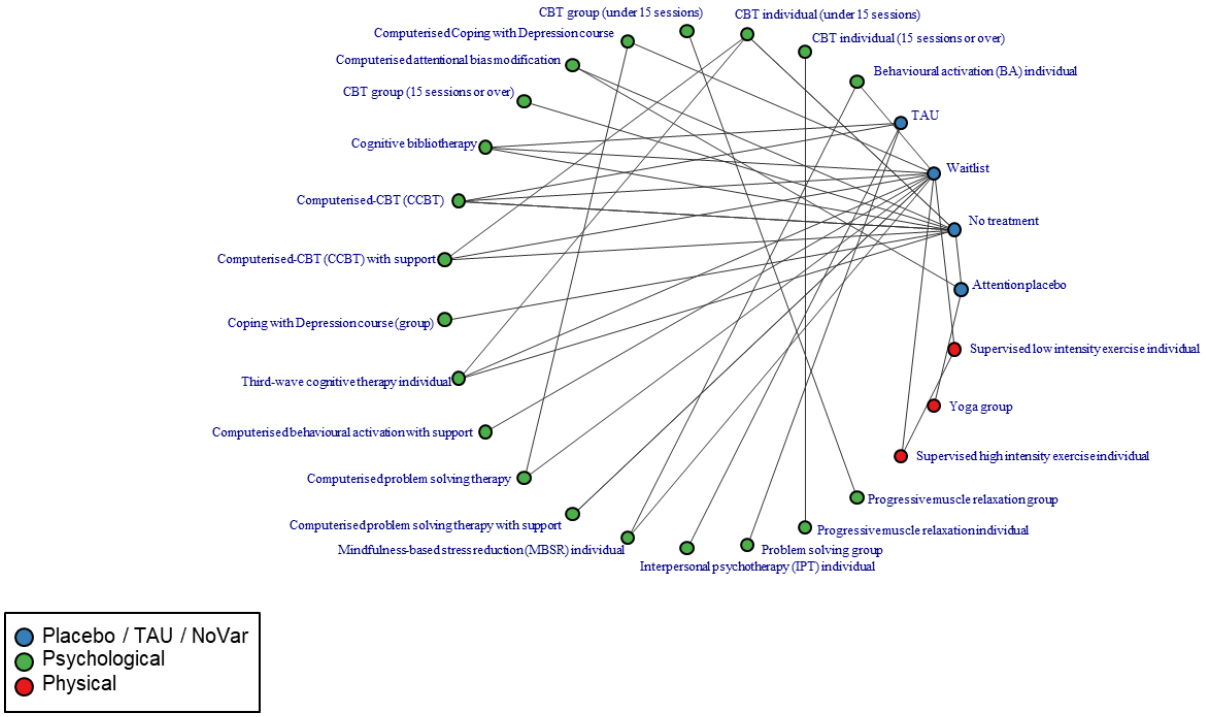
Table 113. Interventions, classes and number of patients (N) included in remission in completers analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	414	Waitlist	1	414	
2	Attention placebo	38	Attention placebo	2	38	
3	No treatment	671	No treatment	3	671	
4	TAU	371	TAU	4	371	
5	Behavioural activation (BA) individual	15	Behavioural therapies individual	5	15	1
6	Coping with Depression course (group)	61	Behavioural therapies group	6	61	1
7	CBT individual (15 sessions or over)	12	Cognitive and cognitive behavioural therapies individual	7	194	1
8	CBT individual (under 15 sessions)	89				
9	Third-wave cognitive therapy individual	93				
10	CBT group (15 sessions or over)	42	Cognitive and cognitive behavioural therapies group	8	107	1
11	CBT group (under 15 sessions)	65				
12	Problem solving group	86	Problem solving group	9	86	1
13	Interpersonal psychotherapy (IPT) individual	58	Interpersonal psychotherapy (IPT) individual	10	58	1
14	Cognitive bibliotherapy	205	Self-help	11	795	2
15	Computerised-CBT (CCBT)	460				
16	Computerised attentional bias modification	28				
17	Computerised Coping with Depression course	51				
18	Computerised problem solving therapy	51				
19	Computerised-CBT (CCBT) with support	133	Self-help with support	12	263	1

20	Computerised behavioural activation with support	40				
21	Computerised problem solving therapy with support	90				
22	Mindfulness-based stress reduction (MBSR) individual	18	Mindfulness or meditation individual	13	18	1
23	Progressive muscle relaxation individual	12	Relaxation individual	14	12	1
24	Progressive muscle relaxation group	61	Relaxation group	15	61	1
25	Supervised high intensity exercise individual	14	Exercise individual	16	29	1
26	Supervised low intensity exercise individual	15				
27	Yoga group	15	Yoga group	17	15	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 73. Network diagram of all studies included in analysis by intervention. Remission in completers.



Without the use of a class network CBT group (under 15 sessions), CBT individual (15 sessions or over), Progressive muscle relaxation group and Progressive muscle relaxation individual would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 74. Network diagram of all studies included in analysis by class. Remission in completers.

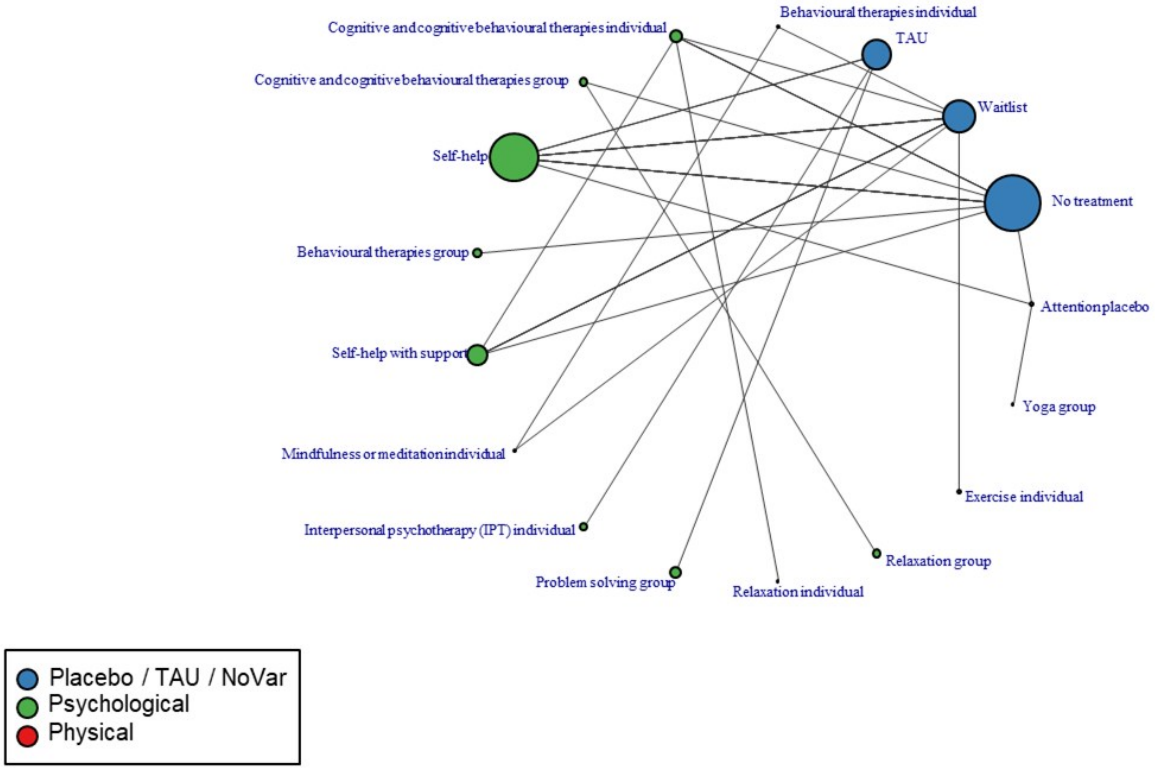
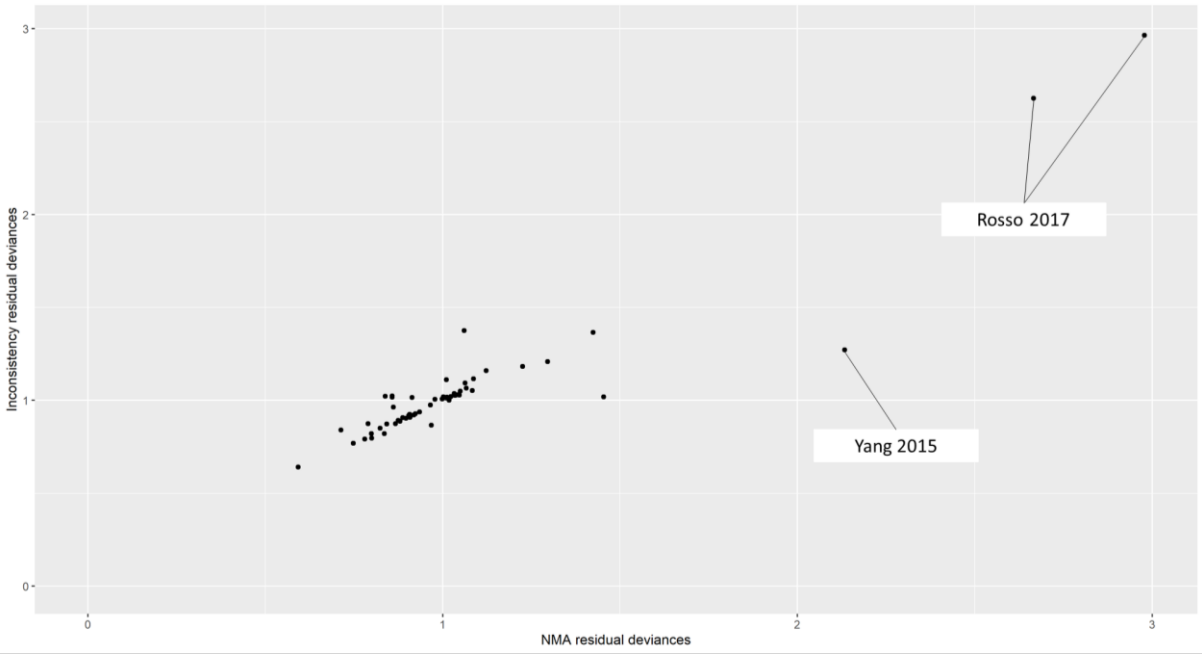


Figure 75. Deviance plot. Remission in completers.



The interventions for which there is evidence of an increased odds of remission compared to TAU are the following (supplement B5, Figure 4.5 in appendix 4):

- CBT individual (under 15 sessions)
- Computerised behavioural activation with support

- Computerised problem solving therapy with support
- Problem solving group
- Supervised high intensity exercise individual
- Supervised low intensity exercise individual
- Third-wave cognitive therapy individual

There is no evidence that any interventions have a decreased odds of remission compared to TAU.

The classes for which evidence suggests an increased odds of remission compared to TAU are the following (supplement B5, Figure 4.6 in appendix 4):

- Exercise individual
- Problem solving group

There is also some evidence to suggest an increased odds of remission for Self-help with support compared to TAU. There is no evidence that any classes have a decreased odds of remission compared to TAU. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Problem solving group is the highest ranked class with a posterior median rank of 1st (95% CrI 1st to 6th). The lowest ranked class is Self-help at 16th (95% CrI 6th to 16th) (Table 114).

The highest ranked intervention is Problem solving group with a posterior median rank of 1st (95% CrI 1st to 5th). The lowest ranked intervention is Attention placebo at 25th (95% CrI 8th to 26th) (Excel file in supplement B6: *"Depression NMA less severe REMIScompleters"*, *"Ranks"* worksheet).

Table 114. Posterior mean and median rank and 95% credible intervals by class. Remission in completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Problem solving group	1.8	1 (1, 6)
Exercise individual	3.5	3 (1, 10)
Yoga group	5.2	3 (1, 15)
Self-help with support	5.7	5 (2, 11)
Cognitive and cognitive behavioural therapies individual	6.2	6 (3, 12)
Behavioural therapies individual	6.4	6 (1, 15)
Mindfulness or meditation individual	7.3	7 (2, 15)
Self-help	8.3	8 (4, 12)
Behavioural therapies group	8.7	9 (3, 15)
Cognitive and cognitive behavioural therapies group	8.9	9 (3, 15)
Interpersonal psychotherapy (IPT) individual	10.9	11 (3, 16)
TAU	11.3	11 (7, 15)
Relaxation group	12.5	14 (3, 16)
Waitlist	12.7	13 (9, 15)
Relaxation individual	13.0	15 (3, 16)
Attention placebo	13.7	15 (6, 16)

Outcome: Remission in those randomised

An additional remission analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients randomised. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 26 trials of 25 interventions and 16 classes were included for this outcome (Table 115, Figure 76, Figure 77).

Posterior mean residual deviances and DIC were similar in the NMA random effects consistency model and the inconsistency model, and there was no clear improvement in the prediction of data in individual studies by the inconsistency model. This suggested that there was no evidence of inconsistency (supplement B5, Table 3.4 in appendix 3; Figure 78). However, both models poorly predicted data from two studies (Yang 2015, Rosso 2017), both of which investigated No treatment compared to an intervention from the Self-help class. The between-study heterogeneity was very similar in consistency and inconsistency models. Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.45$ (95% CrI 0.05 to 1.03)). No treatment was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.7 & 4.8 in appendix 4).

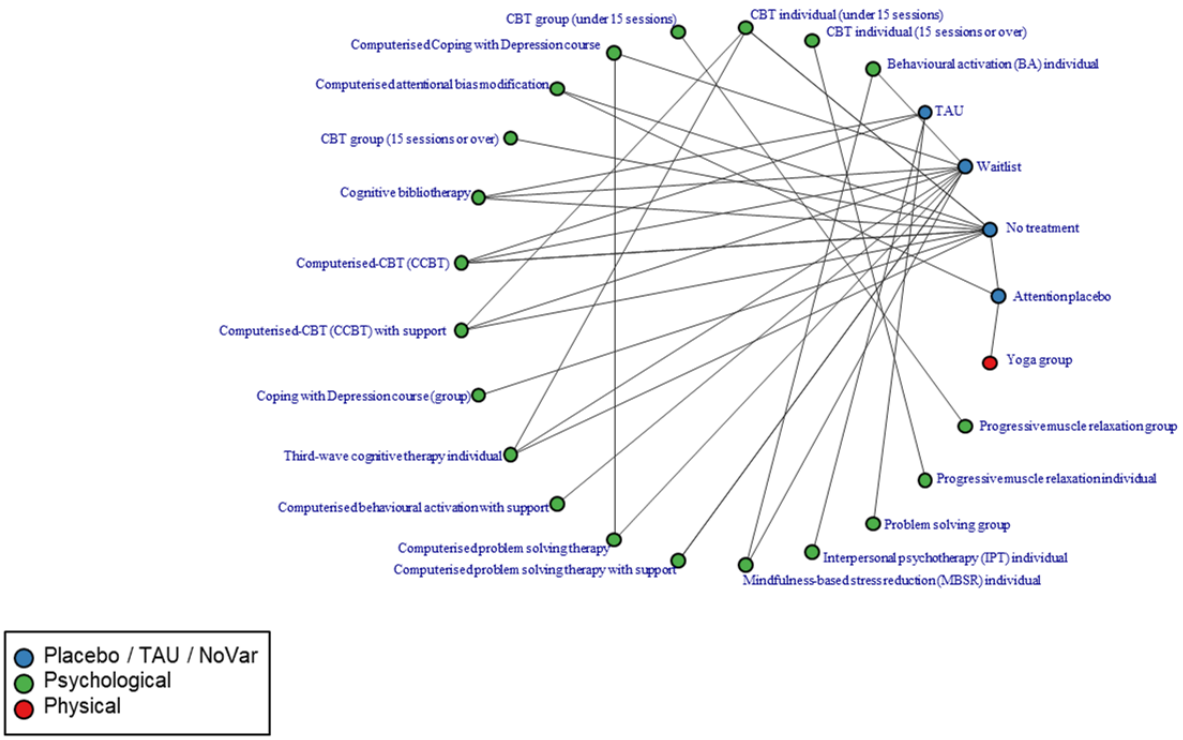
Table 115. Interventions, classes and number of patients (N) included in remission in those randomised analysis.

	Intervention	N	Class		N	Variance Sharing*
1	No treatment	751	Waitlist	1	751	
2	Attention placebo	46	Attention placebo	2	46	
3	Waitlist	468	No treatment	3	468	
4	TAU	437	TAU	4	437	
5	Behavioural activation (BA) individual	16	Behavioural therapies individual	5	16	1
6	Coping with Depression course (group)	68	Behavioural therapies group	6	68	1
7	CBT individual (15 sessions or over)	12	Cognitive and cognitive behavioural therapies individual	7	233	1
8	CBT individual (under 15 sessions)	116				
9	Third-wave cognitive therapy individual	105				
10	CBT group (15 sessions or over)	47	Cognitive and cognitive behavioural therapies group	8	117	1
11	CBT group (under 15 sessions)	70				
12	Problem solving group	89	Problem solving group	9	89	1
13	Interpersonal psychotherapy (IPT) individual	69	Interpersonal psychotherapy (IPT) individual	10	69	1
14	Cognitive bibliotherapy	287	Self-help	11	1050	1
15	Computerised-CBT (CCBT)	559				
16	Computerised attentional bias modification	28				
17	Computerised Coping with Depression course	88				

18	Computerised problem solving therapy	88				
19	Computerised-CBT (CCBT) with support	184	Self-help with support	12	348	1
20	Computerised behavioural activation with support	40				
21	Computerised problem solving therapy with support	124				
22	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	13	20	1
23	Progressive muscle relaxation individual	15	Relaxation individual	14	15	1
24	Progressive muscle relaxation group	63	Relaxation group	15	63	1
25	Yoga group	20	Exercise individual	16	20	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 76. Network diagram of all studies included in analysis by intervention. Remission in those randomised.



Without the use of a class network CBT group (under 15 sessions), CBT individual (15 sessions or over), Progressive muscle relaxation group and Progressive muscle relaxation individual would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 77. Network diagram of all studies included in analysis by class. Remission in those randomised.

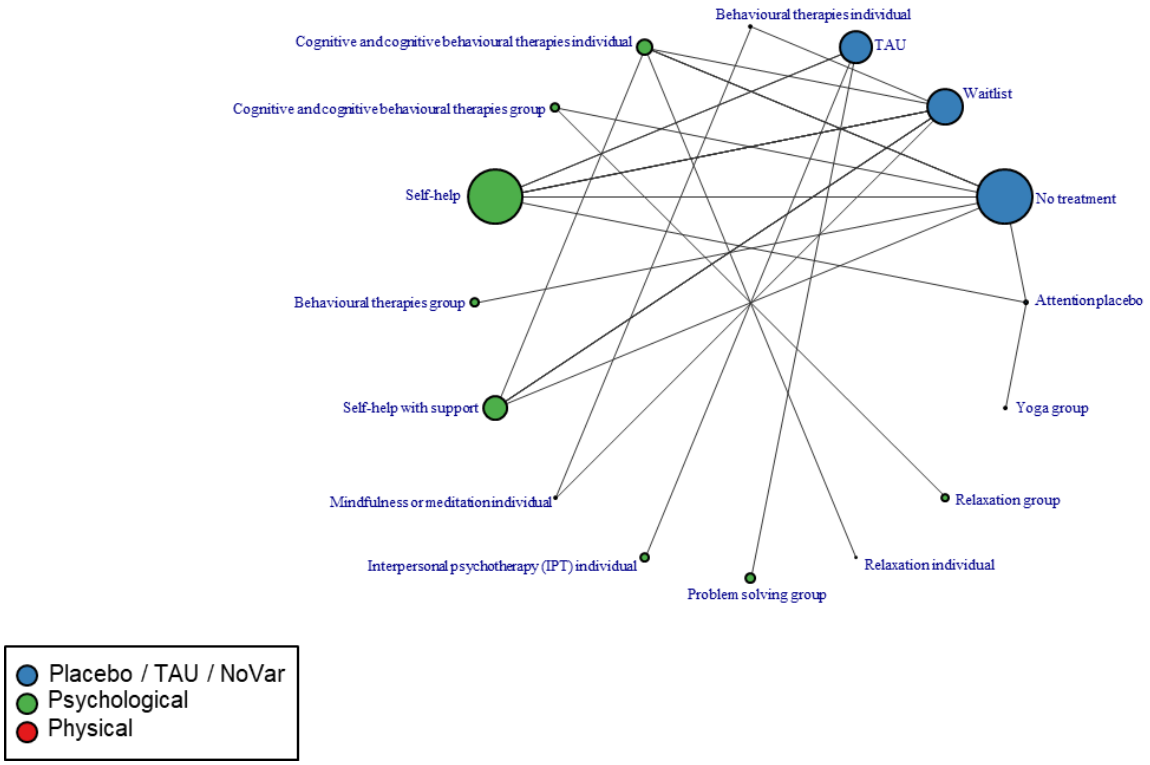
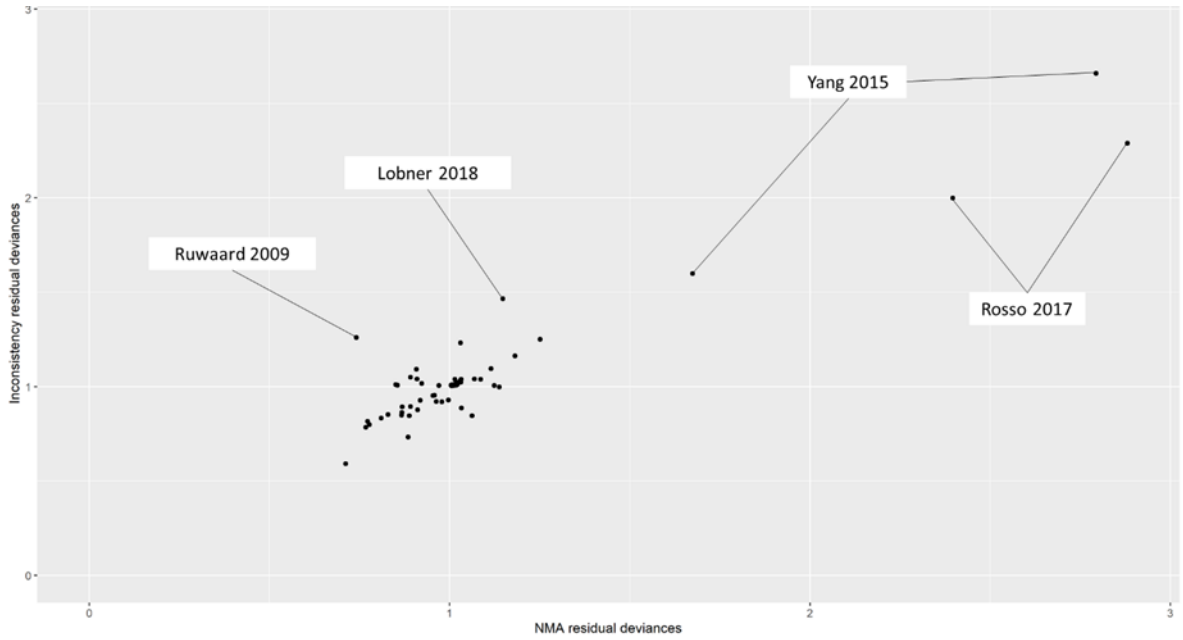


Figure 78. Deviance plot. Remission in those randomised.



The only intervention for which there is evidence of an increased odds of remission compared to TAU is Problem solving group (OR: 28.79; 95%CrI: 7.32, 117.92) (supplement B5, Figure 4.7 in appendix 4). The high efficacy shown here was driven by results from one study (Vazquez 2013/Otero 2015/Lopez 2020) with 173 participants randomised. Problem solving group is the only intervention in its class, which explains why this is also the only class for which there is evidence of increased odds of remission compared to TAU (supplement B5, Figure 4.8 in appendix 4). There was no evidence that any intervention or class had a decreased odds of remission compared to TAU.

Problem solving group is the highest ranked class at 1st (95% CrI 1st to 5th) (Table 116). The highest ranked intervention, Problem solving group (1st, 95% CrI 1st to 5th), is the only treatment within this class (Excel file in supplement B6: *"Depression NMA less severe REMISitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Relaxation individual (15th, 95% CrI 5th to 15th), and the lowest ranked intervention is Progressive muscle relaxation individual (24th, 95% CrI 9th to 24th), which is the only intervention in the Relaxation individual class.

Table 116. Posterior mean and median rank and 95% credible intervals by class. Remission in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Problem solving group	1.6	1 (1, 5)
Yoga group	4.6	3 (1, 14)
Cognitive and cognitive behavioural therapies individual	5.4	5 (2, 11)
Behavioural therapies individual	5.5	4 (1, 13)
Self-help with support	5.7	6 (2, 10)
Mindfulness or meditation individual	6.6	6 (2, 14)
Cognitive and cognitive behavioural therapies group	7	7 (2, 13)
Behavioural therapies group	7.5	7 (2, 14)
Self-help	7.7	8 (4, 11)
Interpersonal psychotherapy (IPT) individual	9.8	10 (3, 15)
TAU	10.3	10 (5, 14)
Relaxation group	10.5	12 (2, 15)

Outcome: Response in completers

As mentioned in the methods section, this analysis included trials reporting three types of data:

a) Number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline

b) Mean change from baseline (CFB), the standard deviation in CFB and the total number of individuals in that arm

c) Baseline and endpoint means, standard deviations, and number of individuals, for each arm of the study

The response analysis was first carried out only in those who completed treatment, using WinBUGS code given in supplement B5, appendix 1. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 12 trials reported response. Out of the remaining studies, 8 reported change from baseline in completers (but not response) and 56 reported baseline and final scores in completers (but not response or change from baseline). This meant that 76 trials of 56 interventions and 27 classes were included in the analysis for this outcome (Table 117, Figure 79, Figure 80).

Although posterior mean residual deviances were very similar between the random-effects NMA consistency model and the inconsistency model, between-study heterogeneity was considerably lower in the inconsistency model, and prediction of some data points was substantially improved in the inconsistency model (supplement B5, Table 3.5 in appendix 3; Figure 81). These were strongly suggestive of inconsistency, particularly in 4 studies

comparing Waitlist, No treatment, Behavioural activation (BA) group and CBT group (under 15 sessions) (Zemestani 2016, Yang 2018, Gordon 1987, Zemstani 2017).

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling treatments was estimated to be 0.66 (95%CrI -0.95, 2.35). The between study heterogeneity was substantially reduced (supplement B5, Table 3.5 in appendix 3), though it had a wide 95%CrI, and the prediction of data points improved such that these were similar between the bias-adjusted consistency NMA and the inconsistency model. This suggests that heterogeneity and inconsistency could be explained by small study effects. However, the residual deviance and DIC were similar between the base-case and bias-adjusted models, and for this reason the base-case model was selected. Results are therefore based on the random-effects consistency NMA model. Results from the base-case unadjusted model and from the bias-adjusted model can be found in Excel files in supplement B6 (*"Depression NMA less severe RESPcompleters base-case.xlsx" and "Depression NMA less severe RESPcompleters bias-adjusted.xlsx"*, respectively).

High between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.96$ (95% CrI 0.71 to 1.28)). Waitlist was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.9 & 4.10 in appendix 4).

Table 117. Interventions, classes and number of patients (N) included in response in completers analysis.

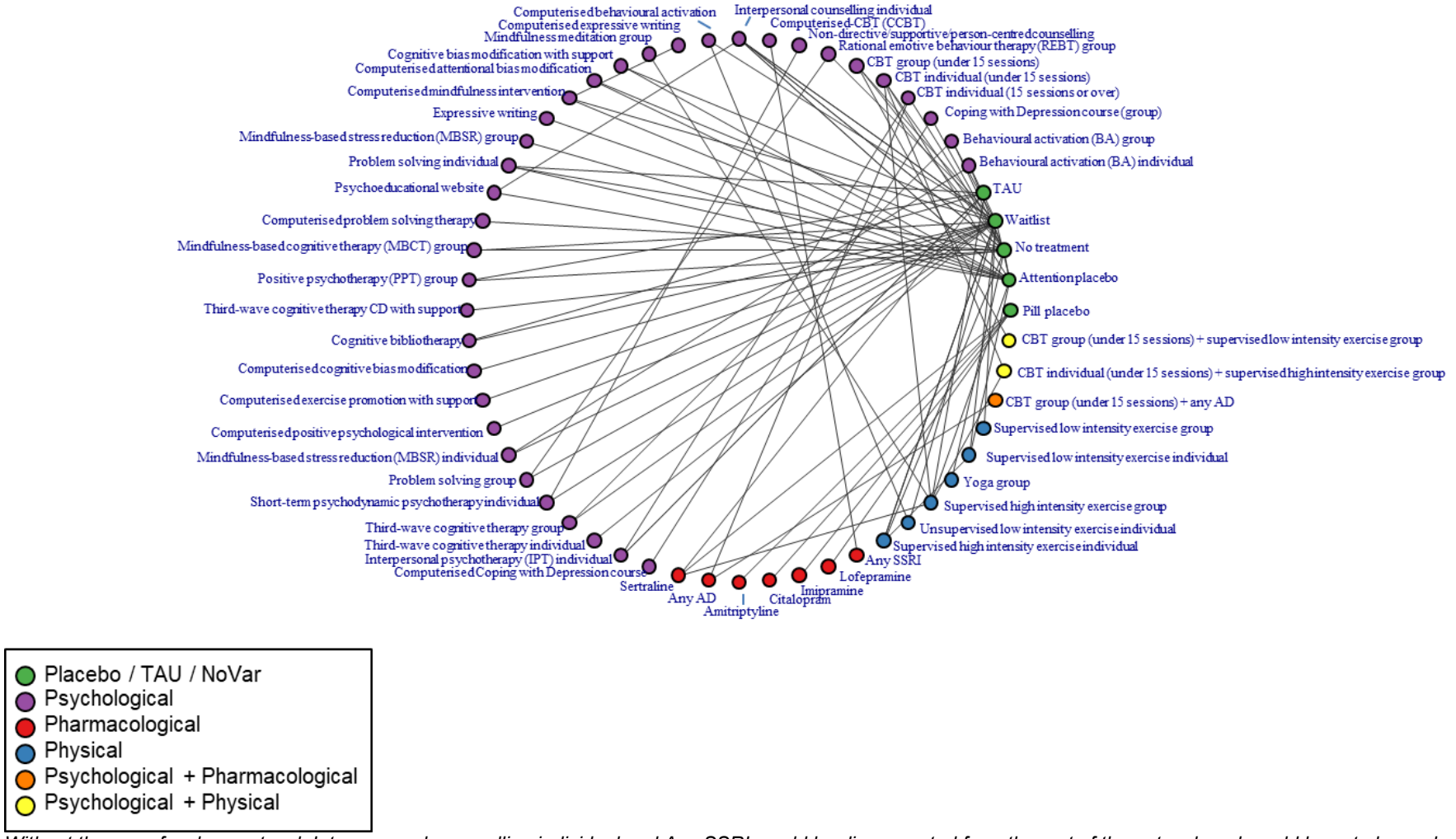
	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	772	Waitlist	1	772	
2	Pill placebo	219	Placebo	2	219	
3	Attention placebo	417	Attention placebo	3	417	
4	No treatment	1033	No treatment	4	1033	
5	TAU	395	TAU	5	395	
6	Behavioural activation (BA) individual	111	Behavioural therapies individual	6	111	1
7	Behavioural activation (BA) group	47	Behavioural therapies group	7	171	1
8	Coping with Depression course (group)	124				
9	CBT individual (15 sessions or over)	68	Cognitive and cognitive behavioural therapies individual	8	361	1
10	CBT individual (under 15 sessions)	233				
11	Third-wave cognitive therapy individual	60				
12	CBT group (under 15 sessions)	59	Cognitive and cognitive behavioural therapies group	9	164	1
13	Positive psychotherapy (PPT) group	76				
14	Rational emotive behaviour therapy (REBT) group	14				
15	Third-wave cognitive therapy group	15				

16	Problem solving individual	98	Problem solving individual	10	98	1
17	Problem solving group	15	Problem solving group	11	15	1
18	Non-directive/supportive/person-centred counselling	39	Counselling individual	12	39	1
19	Interpersonal counselling individual	17	Interpersonal psychotherapy (IPT) individual	13	142	1
20	Interpersonal psychotherapy (IPT) individual	125				
21	Cognitive bibliotherapy	137	Self-help	14	1508	2
22	Computerised-CBT (CCBT)	607				
23	Computerised attentional bias modification	76				
24	Computerised behavioural activation	122				
25	Computerised cognitive bias modification	20				
26	Computerised Coping with Depression course	67				
27	Computerised expressive writing	36				
28	Computerised mindfulness intervention	174				
29	Computerised positive psychological intervention	95				
30	Computerised problem solving therapy	25				
31	Expressive writing	13				
32	Psychoeducational website	136				
33	Cognitive bias modification with support	20	Self-help with support	15	327	3
34	Computerised exercise promotion with support	24				
35	Third-wave cognitive therapy CD with support	283				
36	Short-term psychodynamic psychotherapy individual	43	Short-term psychodynamic psychotherapies individual	16	43	1
37	Mindfulness-based stress reduction (MBSR) individual	18	Mindfulness or meditation individual	17	18	1
38	Mindfulness-based cognitive therapy (MBCT) group	73	Mindfulness or meditation group	18	179	1
39	Mindfulness-based stress reduction (MBSR) group	15				
40	Mindfulness meditation group	91				
41	Any SSRI	24	SSRIs	19	98	4
42	Citalopram	24				
43	Sertraline	50				
44	Amitriptyline	62	TCAs	20	146	4
45	Imipramine	61				
46	Lofepramine	23				

47	Any AD	50	Any AD	21	50	4
48	Supervised high intensity exercise individual	43	Exercise individual	22	189	3
49	Supervised low intensity exercise individual	25				
50	Unsupervised low intensity exercise individual	121				
51	Supervised high intensity exercise group	136	Exercise group	23	178	3
52	Supervised low intensity exercise group	42				
53	Yoga group	40	Yoga group	24	40	1
54	CBT group (under 15 sessions) + any AD	32	Cognitive and cognitive behavioural therapies group + AD	25	32	1
55	CBT individual (under 15 sessions) + supervised high intensity exercise group	18	Cognitive and cognitive behavioural therapies individual + exercise group	26	18	1
56	CBT group (under 15 sessions) + supervised low intensity exercise group	25	Cognitive and cognitive behavioural therapies group + exercise group	27	25	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 79: Network diagram of all studies included in analysis by intervention. Response in Completers.



Without the use of a class network Interpersonal counselling individual and Any SSRI would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 80. Network diagram of all studies included in analysis by class. Response in Completers.

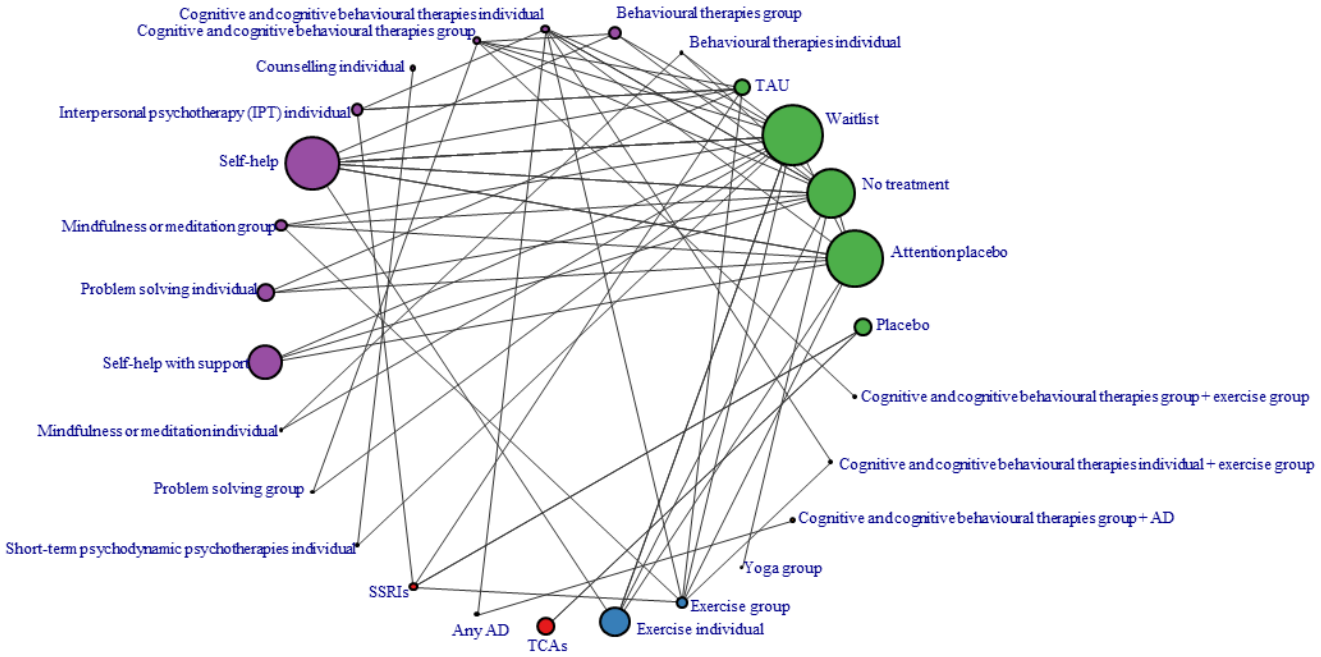
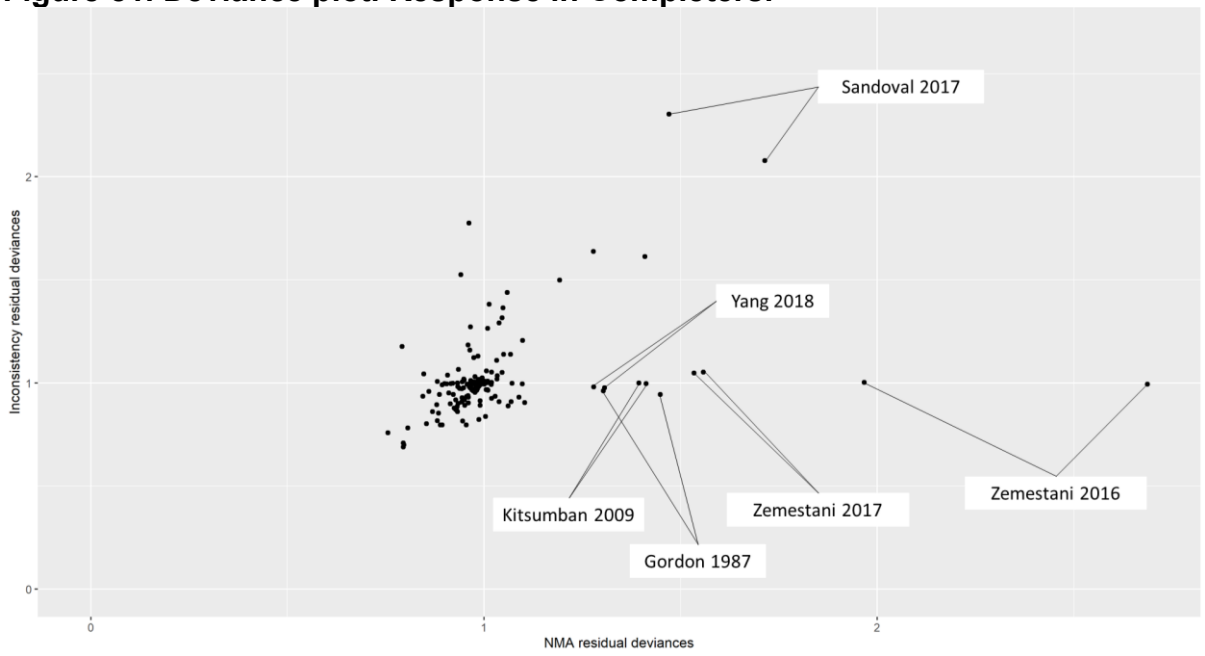


Figure 81. Deviance plot. Response in Completers.



There is evidence of an increased odds of response in completers compared to TAU for the following interventions (supplement B5, Figure 4.9 in appendix 4):

- Amitriptyline
- Behavoural activation (BA) group
- CBT group (under 15 sessions)
- CBT group (under 15 sessions) + supervised low intensity exercise group
- CBT individual (under 15 sessions)
- Imipramine
- Lofepramine
- Mindfulness-based cognitive therapy (MBCT) group
- Mindfulness meditation group
- Pill placebo
- Positive psychotherapy (PPT) group
- Rational emotive behaviour therapy (REBT) group
- Sertraline
- Third-wave cognitive therapy group
- Yoga group

There is no evidence of a reduction in the odds of response for any interventions compared to TAU.

The classes for which there is evidence of an increased odds of response compared to TAU are the following (supplement B5, Figure 4.10 in appendix 4):

- Cognitive and cognitive behavioural therapies group
- Cognitive and cognitive behavioural therapies group + exercise group
- Pill placebo
- TCAs

There is no evidence of any classes having a decreased odds of response compared to TAU. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Cognitive and cognitive behavioural therapies group + exercise group is the highest ranked class with a posterior median rank of 1st (95% CrI 1st to 6th) (Table 118). CBT group (under 15 sessions) + supervised low intensity exercise group is the only intervention in this class, and it is also the highest ranked intervention at 1st (95% CrI 1st to 4th) (Excel file in supplement B6: *"Depression NMA less severe RESPcompleters base-case.xlsx"*, *"Ranks"* worksheet). Cognitive and cognitive behavioural therapies group is the second highest ranked class at 4th (95% CrI 2nd to 12th). The lowest ranked class and intervention is Waitlist, with a posterior median class rank of 24th (95% CrI 20th to 25th) and a posterior median intervention rank of 51st (95% CrI 48th to 52nd). The lowest ranked active class is Problem solving individual at 20th (95% CrI 5th to 25th) (Table 118).

Table 118. Posterior mean and median rank and 95% credible intervals by class. Response in Completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Cognitive and cognitive behavioural therapies group + exercise group	1.5	1 (1, 6)
Cognitive and cognitive behavioural therapies group	5	4 (2, 12)
TCAs	6.1	5 (1, 19)
Yoga group	8.1	6 (1, 24)
Placebo	9.2	8 (3, 21)
Behavioural therapies group	9.7	9 (2, 21)
Problem solving group	10.6	9 (2, 25)
SSRIs	11.3	10 (3, 23)
Cognitive and cognitive behavioural therapies group + AD	11.6	10 (1, 25)
Behavioural therapies individual	11.9	11 (2, 24)
Mindfulness or meditation individual	12.2	11 (2, 25)
Cognitive and cognitive behavioural therapies individual	12.4	12 (4, 22)
Mindfulness or meditation group	12.5	12 (4, 22)
Short-term psychodynamic psychotherapies individual	12.9	12 (2, 25)
Interpersonal psychotherapy (IPT) individual	13.9	14 (4, 24)
Exercise group	14.3	14 (6, 23)
Counselling individual	14.6	15 (2, 25)
Exercise individual	15.3	15 (7, 23)
Self-help with support	16.1	16 (7, 24)
Self-help	16.2	16 (10, 21)
Cognitive and cognitive behavioural therapies individual + exercise group	16.3	18 (3, 25)
Problem solving individual	18.7	20 (5, 25)
Attention placebo	20.1	20 (15, 24)
TAU	21.1	21 (15, 25)
Waitlist	23.6	24 (20, 25)

Outcome: Response in those randomised

The response analysis was also carried out in all patients randomized, including those who discontinued treatment, using WinBUGS code given in supplement B5, appendix 1.

After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 11 trials reported response. A continuity correction was applied to data in 1 of these studies containing a zero cell to stabilize the results. From other studies in the dataset, 6 reported change from baseline (but not response) and 58 reported baseline and final scores (but not response or change from baseline). This meant that 75 trials of 53 interventions and 26 classes were included in the analysis for this outcome (Table 119, Figure 82, Figure 83). Any AD, Mindfulness group + AD, Non-directive/supportive/person-centred counselling and Short-term psychodynamic psychotherapy individual were disconnected from the network, so studies comparing these treatments were excluded.

No evidence of inconsistency was identified with the NMA model having a similar posterior mean residual deviance and lower DIC and between study heterogeneity (supplement B5, Table 3.6 in appendix 3). The inconsistency model did not predict the data substantially better for any data points, although both consistency and inconsistency models provided a poor fit for Zemestani 2016, which compared Waitlist, Behavioural activation (BA) group and Third-wave cognitive therapy group (Figure 84). Reported results are therefore based on the random-effects NMA model, assuming consistency. High between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.76\ (95\%\ \mathrm{CrI}\ 0.55\ \mathrm{to}\ 1.01)$). No treatment was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.11 & 4.12 in appendix 4).

Table 119. Interventions, classes and number of patients (N) included in response in those randomised analysis.

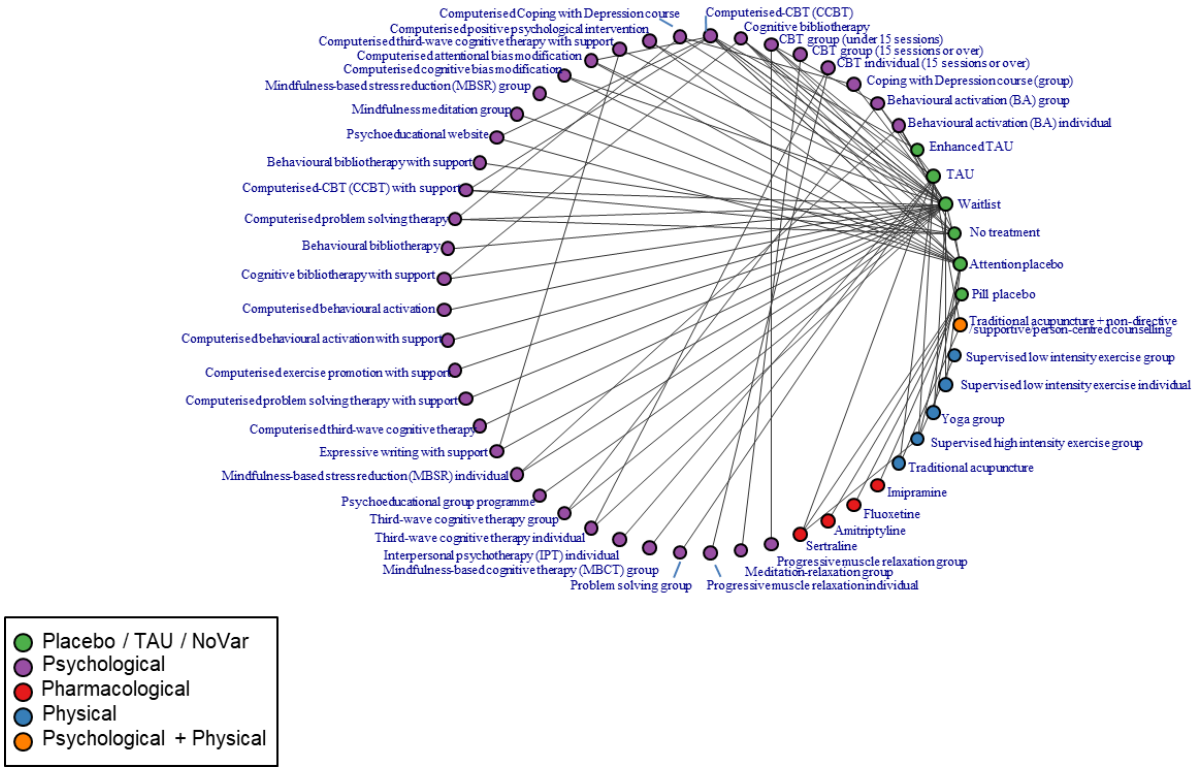
	Intervention	N	Class		N	Variance Sharing*
1	Waitlist	3144	Waitlist	1	3144	
2	Pill placebo	303	Placebo	2	303	
3	Attention placebo	727	Attention placebo	3	727	
4	No treatment	718	No treatment	4	718	
5	TAU	623	TAU	5	623	
6	Enhanced TAU	36	Enhanced TAU	6	36	
7	Behavioural activation (BA) individual	65	Behavioural therapies individual	7	65	1
8	Behavioural activation (BA) group	85	Behavioural therapies group	8	184	1
9	Coping with Depression course (group)	99				
10	CBT individual (15 sessions or over)	56	Cognitive and cognitive behavioural therapies individual	9	121	1
11	Third-wave cognitive therapy individual	65				
12	CBT group (15 sessions or over)	10	Cognitive and cognitive behavioural therapies group	10	341	1
13	CBT group (under 15 sessions)	267				

14	Third-wave cognitive therapy group	64				
15	Problem solving group	89	Problem solving group	11	89	1
16	Interpersonal psychotherapy (IPT) individual	69	Interpersonal psychotherapy (IPT) individual	12	69	1
17	Psychoeducational group programme	22	Psychoeducation group	13	22	1
18	Behavioural bibliotherapy	13	Self-help	14	4373	2
19	Cognitive bibliotherapy	516				
20	Computerised-CBT (CCBT)	2541				
21	Computerised attentional bias modification	181				
22	Computerised behavioural activation	10				
23	Computerised cognitive bias modification	55				
24	Computerised Coping with Depression course	190				
25	Computerised positive psychological intervention	439				
26	Computerised problem solving therapy	232				
27	Computerised third-wave cognitive therapy	31				
28	Psychoeducational website	165				
29	Behavioural bibliotherapy with support	67	Self-help with support	15	849	3
30	Cognitive bibliotherapy with support	125				
31	Computerised-CBT (CCBT) with support	262				
32	Computerised behavioural activation with support	40				
33	Computerised exercise promotion with support	24				
34	Computerised problem solving therapy with support	124				
35	Computerised third-wave cognitive therapy with support	82				
36	Expressive writing with support	125				
37	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	16	20	1
38	Meditation-relaxation group	13	Mindfulness or meditation group	17	197	1
39	Mindfulness-based cognitive therapy (MBCT) group	76				
40	Mindfulness-based stress reduction (MBSR) group	70				
41	Mindfulness meditation group	38				
42	Progressive muscle relaxation individual	15	Relaxation individual	18	15	1

43	Progressive muscle relaxation group	63	Relaxation group	19	63	1
44	Fluoxetine	78	SSRIs	20	159	4
45	Sertraline	81				
46	Amitriptyline	90	TCAs	21	163	4
47	Imipramine	73				
48	Traditional acupuncture	40	Acupuncture	22	40	1
49	Supervised low intensity exercise individual	71	Exercise individual	23	71	3
50	Supervised high intensity exercise group	42	Exercise group	24	52	3
51	Supervised low intensity exercise group	10				
52	Yoga group	65	Yoga group	25	65	1
53	Traditional acupuncture + non-directive/supportive/person-centred counselling	40	Acupuncture + counselling individual	26	40	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 82. Network diagram of all studies included in analysis by intervention. Response in those randomised.



Without the use of a class network CBT group (15 sessions or over) and Meditation-relaxation group would be disconnected from the rest of the network and would have to be excluded from the analysis. Any AD, Mindfulness group + AD, Non-directive/supportive/person-centred counselling and Short-term psychodynamic psychotherapy individual were excluded from the NMA as they were disconnected from the network.

Figure 83. Network diagram of all studies included in analysis by class. Response in those randomised.

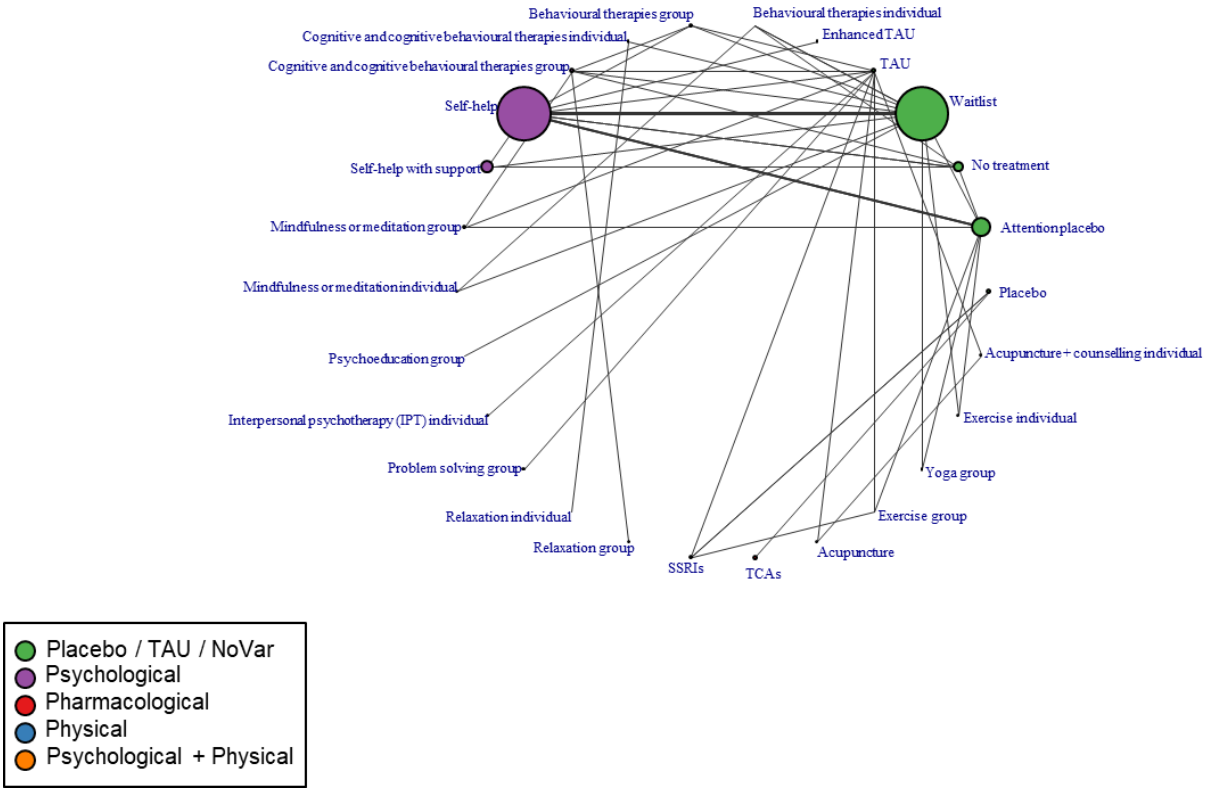
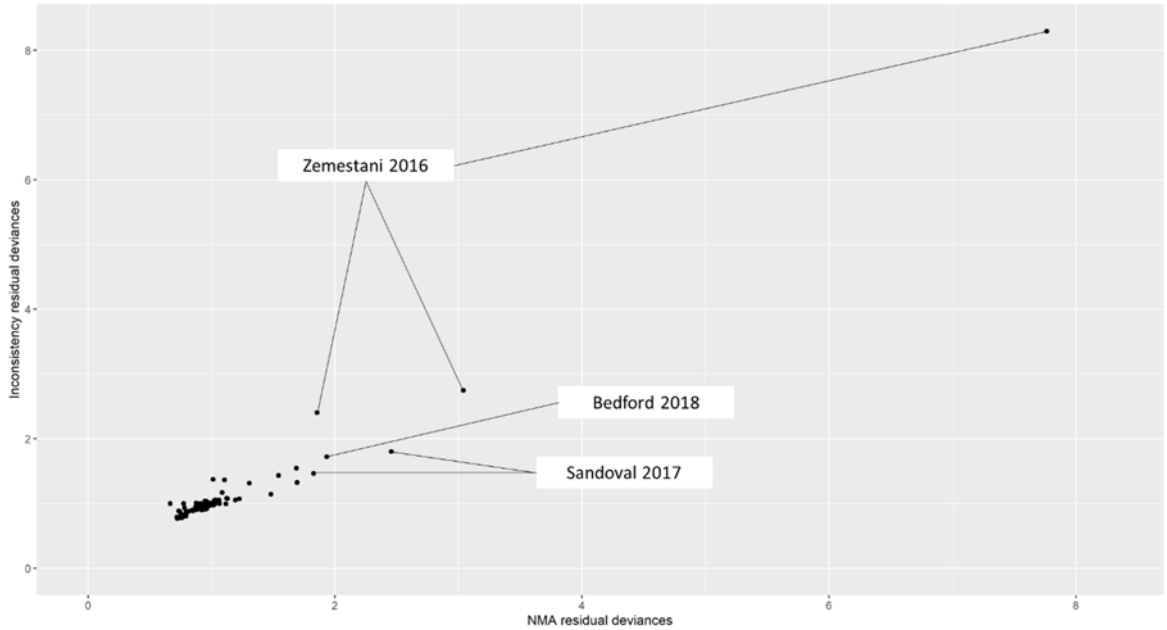


Figure 84. Deviance plot. Response in those randomised.



There is evidence of an increased odds of response compared to TAU for the following interventions (supplement B5, Figure 4.11 in appendix 4):

- Amitriptyline
- Behavioural activation (BA) group
- Behavioural activation (BA) individual
- CBT group (under 15 sessions)

- Fluoxetine
- Imipramine
- Pill placebo
- Problem solving group
- Sertraline
- Supervised high intensity exercise group
- Third-wave cognitive therapy group
- Traditional acupuncture + non-directive/supportive/person-centred counselling

There was no evidence that any interventions had a lower odds of response compared to TAU.

The classes for which there is evidence of an increased odds of response compared to TAU are the following (supplement B5, Figure 4.12 in appendix 4):

- Cognitive and cognitive behavioural therapies group
- Exercise group
- Pill placebo
- Problem solving group
- TCAs

There was no evidence that any class had a lower odds of response compared to TAU. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Whilst there was considerable uncertainty in rankings, TCAs and Problem solving group had the highest posterior median rank (3rd, 95% CrI 1st to 20th and 3rd, 95% CrI 1st to 18th respectively). The highest ranked intervention is Amitryptiline with a posterior median rank of 3rd (95% CrI 1st to 38th) (Excel file in supplement B6: *"Depression NMA less severe RESPitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked classes are Waitlist (22nd, 95% CrI 18th to 25th) and Relaxation individual (25th, 95% CrI 4th to 25th) (Table 120).

Table 120. Posterior mean and median rank and 95% credible intervals by class. Response in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
TCAs	4.5	3 (1, 20)
Problem solving group	4.9	3 (1, 18)
SSRIs	6.3	5 (1, 21)
Placebo	6.8	5 (2, 19)
Cognitive and cognitive behavioural therapies group	8.3	8 (2, 18)
Behavioural therapies group	8.9	8 (2, 20)
Exercise group	9.3	9 (2, 20)
Acupuncture + counselling individual	10.3	9 (1, 24)
Behavioural therapies individual	10.4	10 (1, 23)
Yoga group	10.5	10 (1, 24)
Acupuncture	10.8	10 (1, 24)
Mindfulness or meditation individual	11.1	10 (1, 24)
Cognitive and cognitive behavioural therapies individual	12.2	12 (1, 24)

Mindfulness or meditation group	12.8	13 (4, 22)
Exercise individual	14.2	14 (5, 23)
Self-help	15.2	15 (10, 19)
Psychoeducation group	15.4	16 (2, 25)
Self-help with support	15.6	16 (10, 21)
Relaxation group	15.9	17 (2, 25)
Interpersonal psychotherapy (IPT) individual	18.5	20 (4, 25)
Attention placebo	19.1	19 (14, 23)
TAU	19.6	20 (14, 24)
Enhanced TAU	21	22 (11, 25)
Relaxation individual	21.5	25 (4, 25)
Waitlist	22.1	22 (18, 25)

Outcome: SMD

As mentioned in the methods section, this analysis also included trials reporting three types of data:

a) Mean change from baseline (CFB), the standard deviation in CFB and the total number of individuals in that arm

b) Baseline and endpoint means, standard deviations, and number of individuals, for each arm of the study

c) Number of individuals responding to treatment in each arm of each study, out of the total number of individuals, defined as those improving by more than a certain percentage from baseline

This analysis was carried out on all patients randomized where possible, using WinBUGS code given in supplement B5, appendix 1. However, if trials only reported the number of completers then these were also included. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 10 trials reported CFB. Out of the remaining studies, 115 reported baseline and follow-up scores (but not CFB) and 2 reported response (but not CFB or baseline and follow-up). This meant that 127 trials of 76 interventions and 34 classes were included in the analysis for this outcome (Table 121,

Figure 85, Figure 86). Although for other outcomes Interpersonal counselling + AD was incorrectly included in the class of Counselling + AD, for SMD (both less severe and more severe) this intervention was correctly coded in Interpersonal psychotherapy (IPT) individual + AD. Results are therefore shown here for the correct class coding. A post-hoc sensitivity analysis was conducted to assess the impact of this in more severe SMD (Sensitivity analyses: post-hoc).

No evidence of inconsistency was identified with the NMA model having a slightly lower DIC, and similar between study heterogeneity (supplement B5, Table 3.7 in appendix 3). The inconsistency model did not predict the data substantially better for any data points (Figure 87). Between study heterogeneity was lower in the bias-adjusted model that accounted for small study effects (performed as a prespecified sensitivity analysis) (supplement B5, Table 3.7 in appendix 3). The negative bias parameter (-2.96; 95%CrI: -5.11 to -0.91) indicated that smaller studies had larger effects favouring active interventions versus control interventions or counselling. Reported results are therefore based on the bias-adjusted random-effects NMA model, assuming consistency. Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ((*"Depression NMA less severe SMD bias-adjusted.xlsx"* and *"Depression NMA less severe SMD base-case.xlsx"*, respectively).

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.23$ (95% CrI 0.10 to 0.47)). Attention placebo was used as the network reference treatment, as this improved estimation and convergence of the model due to its connectivity. However, relative effects are presented compared to TAU (supplement B5, Figures 4.13 & 4.14 in appendix 4).

Table 121. Interventions, classes and number of patients (N) included in SMD analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Attention placebo	935	Attention placebo	1	935	
2	Pill placebo	301	Placebo	2	301	
3	No treatment	1478	No treatment	3	1478	
4	Waitlist	3555	Waitlist	4	3555	
5	TAU	815	TAU	5	815	
6	Enhanced TAU	36	Enhanced TAU	6	36	
7	Behavioural activation (BA) individual	147	Behavioural therapies individual	7	147	1
8	Behavioural activation (BA) group	117	Behavioural therapies group	8	340	1
9	Coping with Depression course (group)	223				
10	CBT individual (15 sessions or over)	123	Cognitive and cognitive behavioural therapies individual	9	481	1
11	CBT individual (under 15 sessions)	233				
12	Third-wave cognitive therapy individual	125				
13	CBT group (15 sessions or over)	10	Cognitive and cognitive behavioural therapies group	10	480	2
14	CBT group (under 15 sessions)	316				

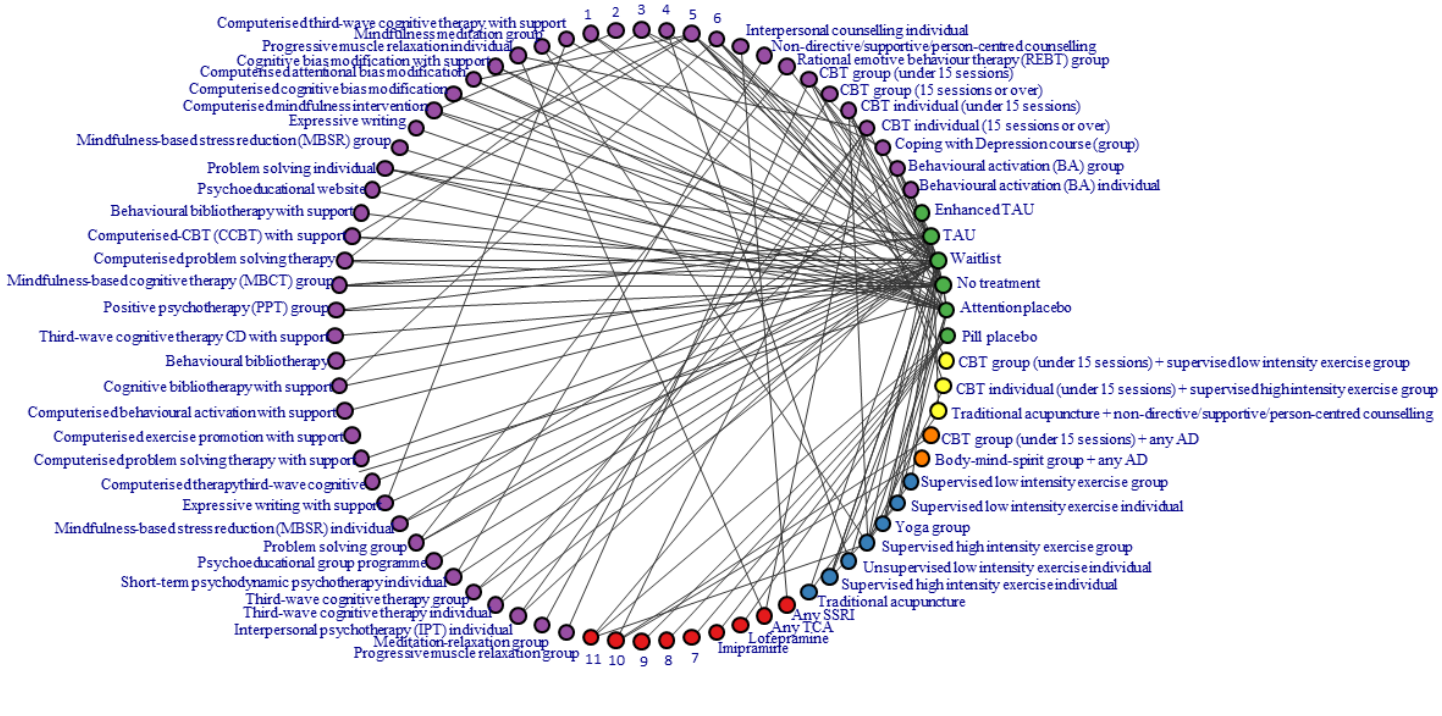
15	Positive psychotherapy (PPT) group	76				
16	Rational emotive behaviour therapy (REBT) group	14				
17	Third-wave cognitive therapy group	64				
18	Problem solving individual	98	Problem solving individual	11	98	1
19	Problem solving group	104	Problem solving group	12	104	1
20	Non-directive/supportive/person-centred counselling	55	Counselling individual	13	55	1
21	Interpersonal counselling individual	17	Interpersonal psychotherapy (IPT) individual	14	153	1
22	Interpersonal psychotherapy (IPT) individual	136				
23	Psychoeducational group programme	22	Psychoeducation group	15	22	1
24	Behavioural bibliotherapy	13	Self-help	16	4922	3
25	Cognitive bibliotherapy	516				
26	Computerised-CBT (CCBT)	2619				
27	Computerised attentional bias modification	230				
28	Computerised behavioural activation	122				
29	Computerised cognitive bias modification	75				
30	Computerised Coping with Depression course	257				
31	Computerised expressive writing	36				
32	Computerised mindfulness intervention	174				
33	Computerised positive psychological intervention	439				
34	Computerised problem solving therapy	232				
35	Computerised third-wave cognitive therapy	31				
36	Expressive writing	13				
37	Psychoeducational website	165				
38	Behavioural bibliotherapy with support	67	Self-help with support	17	1286	4
39	Cognitive bias modification with support	20				
40	Cognitive bibliotherapy with support	125				
41	Computerised-CBT (CCBT) with support	396				
42	Computerised behavioural activation with support	40				

43	Computerised exercise promotion with support	24				
44	Computerised problem solving therapy with support	124				
45	Computerised third-wave cognitive therapy with support	82				
46	Expressive writing with support	125				
47	Third-wave cognitive therapy CD with support	283				
48	Short-term psychodynamic psychotherapy individual	49	Short-term psychodynamic psychotherapies individual	18	49	1
49	Mindfulness-based stress reduction (MBSR) individual	20	Mindfulness or meditation individual	19	20	1
50	Meditation-relaxation group	13	Mindfulness or meditation group	20	376	5
51	Mindfulness-based cognitive therapy (MBCT) group	149				
52	Mindfulness-based stress reduction (MBSR) group	85				
53	Mindfulness meditation group	129				
54	Progressive muscle relaxation individual	13	Relaxation individual	21	13	1
55	Progressive muscle relaxation group	63	Relaxation group	22	63	2
56	Any SSRI	24	SSRIs	23	207	6
57	Citalopram	24				
58	Fluoxetine	78				
59	Sertraline	81				
60	Amitriptyline	67	TCAs	24	136	6
61	Any TCA	10				
62	Imipramine	36				
63	Lofepramine	23				
64	Any AD	65	Any AD	25	65	6
65	Traditional acupuncture	40	Acupuncture	26	40	1
66	Supervised high intensity exercise individual	43	Exercise individual	27	250	7
67	Supervised low intensity exercise individual	86				
68	Unsupervised low intensity exercise individual	121				
69	Supervised high intensity exercise group	147	Exercise group	28	199	8
70	Supervised low intensity exercise group	52				
71	Yoga group	73	Yoga group	29	73	2
72	CBT group (under 15 sessions) + any AD	32	Cognitive and cognitive behavioural therapies group + AD	30	32	1
73	Body-mind-spirit group + any AD	15	Mindfulness or meditation group + AD	31	15	1

74	Traditional acupuncture + non-directive/supportive/person-centred counselling	40	Acupuncture + counselling individual	32	40	1
75	CBT individual (under 15 sessions) + supervised high intensity exercise group	18	Cognitive and cognitive behavioural therapies individual + exercise group	33	18	1
76	CBT group (under 15 sessions) + supervised low intensity exercise group	25	Cognitive and cognitive behavioural therapies group + exercise group	34	25	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 85. Network diagram of all studies included in analysis by intervention. SMD.



1 Computerised positive psychological intervention; 2 Computerised expressive writing; 3 Computerised Coping with Depression course; 4 Computerised behavioural activation; 5 Computerised-CBT (CCBT); 6 Cognitive bibliotherapy; 7 Fluoxetine; 8 Citalopram; 9 Amitriptyline; 10 Any AD; 11 Sertraline
Without the use of a class network CBT group (15 sessions or over), Interpersonal counselling individual, Meditation-relaxation group and Any SSRI would be disconnected from the rest of the network and would have to be excluded from the analysis.

Figure 86. Network diagram of all studies included in analysis by class. SMD.

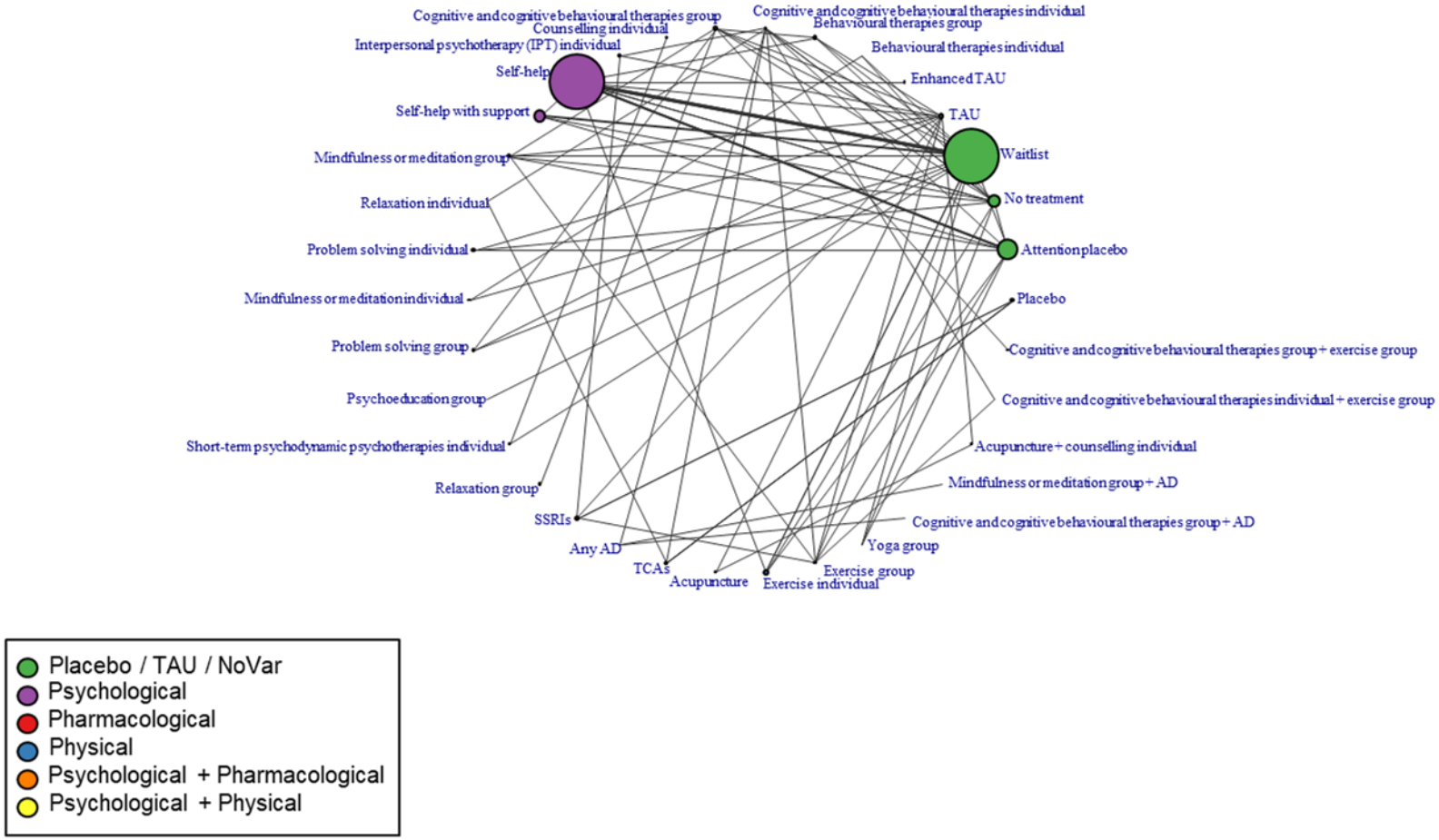
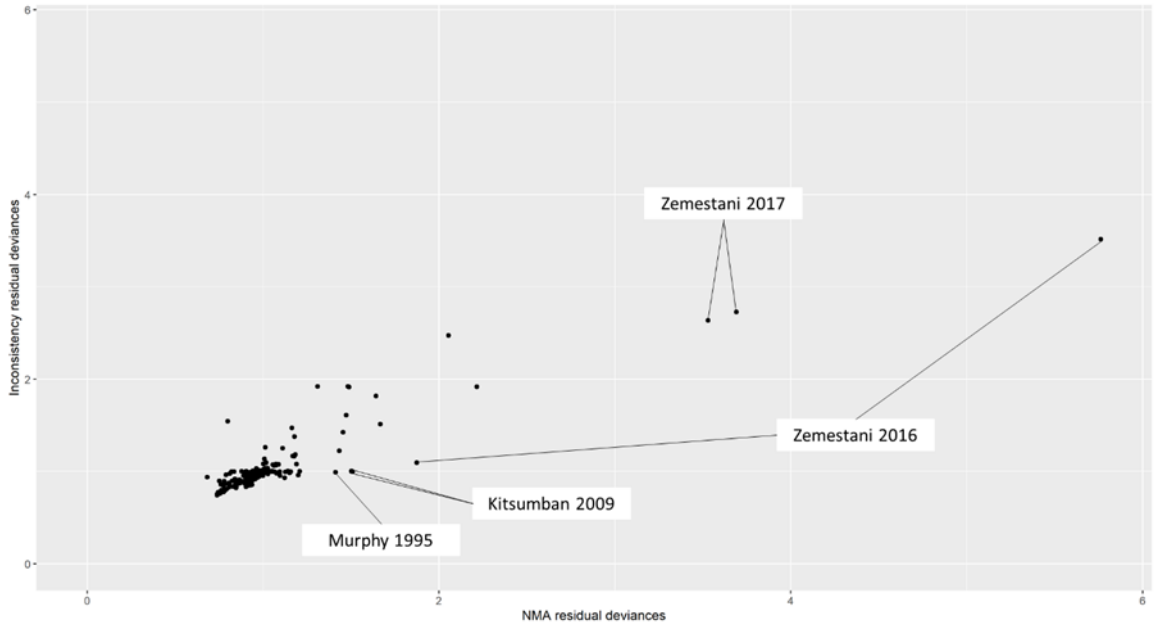


Figure 87. Deviance plot. SMD.



There is evidence of a decreased SMD in depression (lower SMD corresponds to improved outcomes) compared to TAU for the following interventions (supplement B5, Figure 4.13 in appendix 4):

- Behavioural activation (BA) group
- CBT group (under 15 sessions)
- CBT group (under 15 sessions) + supervised low intensity exercise group
- CBT individual (15 sessions or over)
- Meditation-relaxation group
- Mindfulness-based cognitive therapy (MBCT) group
- Mindfulness mediation group
- Positive psychotherapy (PPT) group
- Problem solving group
- Third-wave cognitive therapy CD with support
- Third-wave cognitive therapy group
- Third-wave cognitive therapy individual
- Traditional acupuncture + non-directive/supportive/person-centred counselling

There was no evidence that any interventions have a higher SMD compared to TAU.

The classes for which there is clear evidence suggesting a lower SMD in depression compared to TAU are the following (supplement B5, Figure 4.14 in appendix 4):

- Cognitive and cognitive behavioural therapies group
- Cognitive and cognitive behavioural therapies group + exercise group.

However, there is also some evidence to suggest lower SMD compared to TAU in Cognitive and cognitive behavioural therapies individual, Self-help and Self-help with support.

The only class for which there was some evidence of a higher standardized mean difference compared to TAU is Waitlist. For many classes, effects were more uncertain than at the

intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Cognitive and cognitive behavioural therapies group + exercise group is the highest ranked class with a posterior median rank of 2nd (95% CrI 1st to 14th). This class contained only one intervention, CBT group (under 15 sessions) + supervised low intensity exercise group, which was also the highest ranked intervention (1st, 95% CrI 1st to 6th). The lowest ranked intervention is Waitlist at 44th (95% CrI 42nd to 44th) (Excel file in supplement B6: *"Depression NMA less severe SMD bias-adjusted.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Waitlist, with a posterior median rank of 27th (95% CrI 21st to 31st), and the lowest ranked active class is Problem solving individual (27th, 95% CrI 6th to 32nd) (Table 122).

Table 122. Posterior mean and median rank and 95% credible intervals by class. SMD.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Cognitive and cognitive behavioural therapies group + exercise group	2.919	2 (1, 14)
Problem solving group	6.607	5 (1, 26)
Cognitive and cognitive behavioural therapies group	9.553	9 (3, 22)
Mindfulness or meditation group + AD	12.22	7 (1, 32)
Behavioural therapies group	13.09	12 (3, 28)
Cognitive and cognitive behavioural therapies individual	13.14	12 (4, 27)
TCAs	13.27	12 (3, 29)
Cognitive and cognitive behavioural therapies group + AD	13.34	9 (1, 32)
Acupuncture + counselling individual	13.37	12 (2, 31)
Yoga group	13.83	12 (2, 31)
Acupuncture	14.26	13 (2, 31)
Mindfulness or meditation group	14.47	14 (4, 28)
Behavioural therapies individual	14.72	13 (2, 31)
Placebo	15.09	14 (4, 29)
SSRIs	15.9	15 (4, 30)
Mindfulness or meditation individual	16.09	14 (1, 32)
Short-term psychodynamic psychotherapies individual	16.49	15 (2, 32)
Interpersonal psychotherapy (IPT) individual	16.93	17 (4, 30)
Relaxation group	17.84	18 (3, 32)
Exercise group	17.91	18 (1, 32)
Self-help with support	18.22	18 (11, 25)
Relaxation individual	18.39	19 (1, 32)
Counselling individual	19.2	21 (2, 32)
Exercise individual	19.43	20 (4, 31)
Self-help	19.51	20 (13, 25)
Cognitive and cognitive behavioural therapies individual + exercise group	19.78	22 (2, 32)
Psychoeducation group	20.8	23 (3, 32)
Attention placebo	21.52	22 (14, 28)
Problem solving individual	24.28	27 (6, 32)
TAU	24.35	25 (18, 30)
Enhanced TAU	24.9	26 (11, 32)

Waitlist	26.56	27 (21, 31)

Results for adults with a new episode of more severe depression

Outcome: Discontinuation (for any reason)

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients randomized. After excluding trials with zero events in all arms and trials with the number events equal to the denominator, 402 trials of 74 interventions and 39 classes were included for this outcome (Table 123, methods, under 'Class models'

Figure 88,

Figure 89). A continuity correction was applied to data in 2 studies containing at least one zero cell to stabilize the results.

Although there was lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, the between-study heterogeneity was lower in the inconsistency model (supplement B5, Table 3.8. in appendix 3). The prediction of individual studies was similar in both models, apart from for one study (Sun 2013) (Figure 90). This was for a zero arm to which a continuity correction had been added.

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling treatments was estimated to be -0.35 (95%CrI -0.76, 0.04). The between study heterogeneity was slightly reduced and the DIC was lower than in the base-case consistency model (supplement B5, Table 3.8 in appendix 3). Further details are given under '*Sensitivity Analyses*'. Results from the bias-adjusted model and from the unadjusted base-case consistency model can be found in Excel files in supplement B6 ("*Depression NMA more severe DISCONany bias-adjusted.xlsx*" and *"Depression NMA more severe DISCONany base-case.xlsx"*, respectively).

Reported results are based on the bias-adjusted random effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.28\ (95\%\ \mathrm{CrI}\ 0.22\ \mathrm{to}\ 0.33)$). Pill placebo was used as the network reference treatment, and reported relative effects are presented compared to this (supplement B5, Figures 5.1 & 5.2 in appendix 5).

Table 123. Interventions, classes and number of patients (N) included in Discontinuation (for any reason) analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	16577	Placebo	1	16577	
2	Attention placebo	36	Attention placebo	2	36	
3	No treatment	764	No treatment	3	764	
4	Waitlist	580	Waitlist	4	580	
5	TAU	266	TAU	5	266	
6	Enhanced TAU	37	Enhanced TAU	6	37	
7	Mirtazapine	2637	Mirtazapine	7	2637	
8	Trazodone	1430	Trazodone	8	1430	
9	Behavioural activation (BA) individual	595	Behavioural therapies individual	9	595	1
10	Behavioural activation (BA) group	15	Behavioural therapies group	10	46	1
11	Coping with Depression course (group)	31				
12	CBT individual (15 sessions or over)	461	Cognitive and cognitive behavioural therapies individual	11	771	1
13	CBT individual (under 15 sessions)	287				
14	Third-wave cognitive therapy individual	23				
15	CBT group (under 15 sessions)	162	Cognitive and cognitive behavioural therapies group	12	162	1

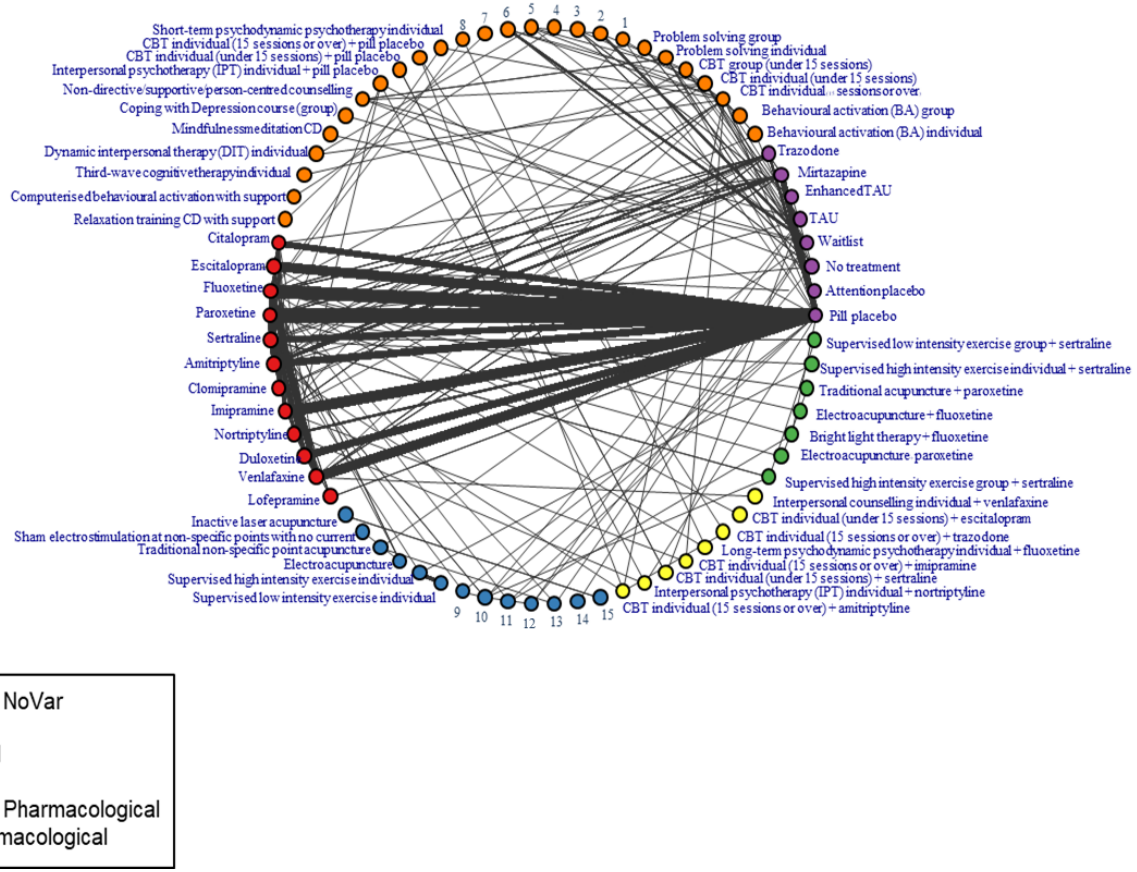
16	Problem solving individual	448	Problem solving individual	13	448	1
17	Problem solving group	58	Problem solving group	14	58	1
18	Non-directive/supportive/person-centred counselling	332	Counselling individual	15	332	1
19	Interpersonal psychotherapy (IPT) individual	63	Interpersonal psychotherapy (IPT) individual	16	63	1
20	Cognitive bibliotherapy	169	Self-help	17	477	2
21	Computerised-CBT (CCBT)	115				
22	Mindfulness meditation CD	39				
23	Psychoeducational website	154				
24	Cognitive bibliotherapy with support	67	Self-help with support	18	556	3
25	Computerised-CBT (CCBT) with support	290				
26	Computerised behavioural activation with support	159				
27	Mindfulness meditation CD with support	20				
28	Relaxation training CD with support	20				
29	Long-term psychodynamic psychotherapy individual	90	Long-term psychodynamic psychotherapies individual	19	90	1
30	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	20	129	1
31	Short-term psychodynamic psychotherapy individual	56				
32	CBT individual (15 sessions or over) + pill placebo	14	Cognitive and cognitive behavioural therapies individual + placebo	21	97	1
33	CBT individual (under 15 sessions) + pill placebo	83				
34	Interpersonal psychotherapy (IPT) individual + pill placebo	48	Interpersonal psychotherapy (IPT) individual + placebo	22	48	1
35	Citalopram	3523	SSRIs	23	28464	4
36	Escitalopram	5627				
37	Fluoxetine	7766				
38	Paroxetine	8362				
39	Sertraline	3186				
40	Amitriptyline	3778	TCAs	24	7782	5
41	Clomipramine	601				
42	Imipramine	2585				

43	Lofepramine	296				
44	Nortriptyline	522				
45	Duloxetine	5226	SNRIs	25	10251	4
46	Venlafaxine	5025				
47	Inactive laser acupuncture	36	Sham acupuncture	26	117	1
48	Sham electrostimulation at non-specific points with no current	29				
49	Traditional non-specific point acupuncture	52				
50	Electroacupuncture	112	Acupuncture	27	255	1
51	Laser acupuncture	41				
52	Traditional acupuncture	102				
53	Supervised high intensity exercise individual	162	Exercise individual	28	336	3
54	Supervised low intensity exercise individual	121				
55	Unsupervised high intensity exercise individual	53				
56	Supervised high intensity exercise group	124	Exercise group	29	167	3
57	Supervised low intensity exercise group	43				
58	Yoga group	30	Yoga group	30	30	1
59	Bright light therapy	32	Light therapy	31	32	1
60	CBT individual (15 sessions or over) + amitriptyline	50	Cognitive and cognitive behavioural therapies individual + AD	32	246	6
61	CBT individual (15 sessions or over) + imipramine	25				
62	CBT individual (15 sessions or over) + trazodone	11				
63	CBT individual (under 15 sessions) + escitalopram	52				
64	CBT individual (under 15 sessions) + sertraline	108				
65	Long-term psychodynamic psychotherapy individual + fluoxetine	91	Long-term psychodynamic psychotherapy individual + AD	33	91	6
66	Interpersonal psychotherapy (IPT) individual + nortriptyline	16	Interpersonal psychotherapy (IPT) individual + AD	34	16	6
67	Interpersonal counselling individual + venlafaxine	13	Counselling individual + AD	35	13	6
68	Supervised high intensity exercise individual + sertraline	84	Exercise individual + AD	36	84	6
69	Supervised high intensity exercise group + sertraline	97	Exercise group + AD	37	134	6
70	Supervised low intensity exercise group + sertraline	37				
71	Electroacupuncture + fluoxetine	48	Acupuncture + AD	38	160	1

72	Electroacupuncture + paroxetine	58				
73	Traditional acupuncture + paroxetine	54				
74	Bright light therapy + fluoxetine	29	Light therapy + AD	39	29	1

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 88. Network diagram of all studies included in analysis by intervention. Discontinuation (for any reason).



1 Interpersonal psychotherapy (IPT) individual; 2 Cognitive bibliotherapy; 3 Computerised CBT (CCBT); 4 Psychoeducational website; 5 Cognitive bibliotherapy with support; 6 Computerised CBT with support; 7 Mindfulness meditation CD with support; 8 Long-term psychodynamic therapy individual; 9 Unsupervised high intensity exercise individual; 10 Supervised high intensity exercise group; 11 Supervised low intensity exercise group; 12 Bright light therapy; 13 Traditional acupuncture; 14 Yoga group; 15 Laser acupuncture
Without the use of a class network the following treatments would be disconnected from the rest of the network and would have to be excluded from the analysis: Psychoeducational website, Mindfulness meditation CD with support, Inactive laser acupuncture, Computerised behavioural activation with support, Relaxation training CD with support, and Laser acupuncture

Figure 89. Network diagram of all studies included in analysis by class. Discontinuation (for any reason).

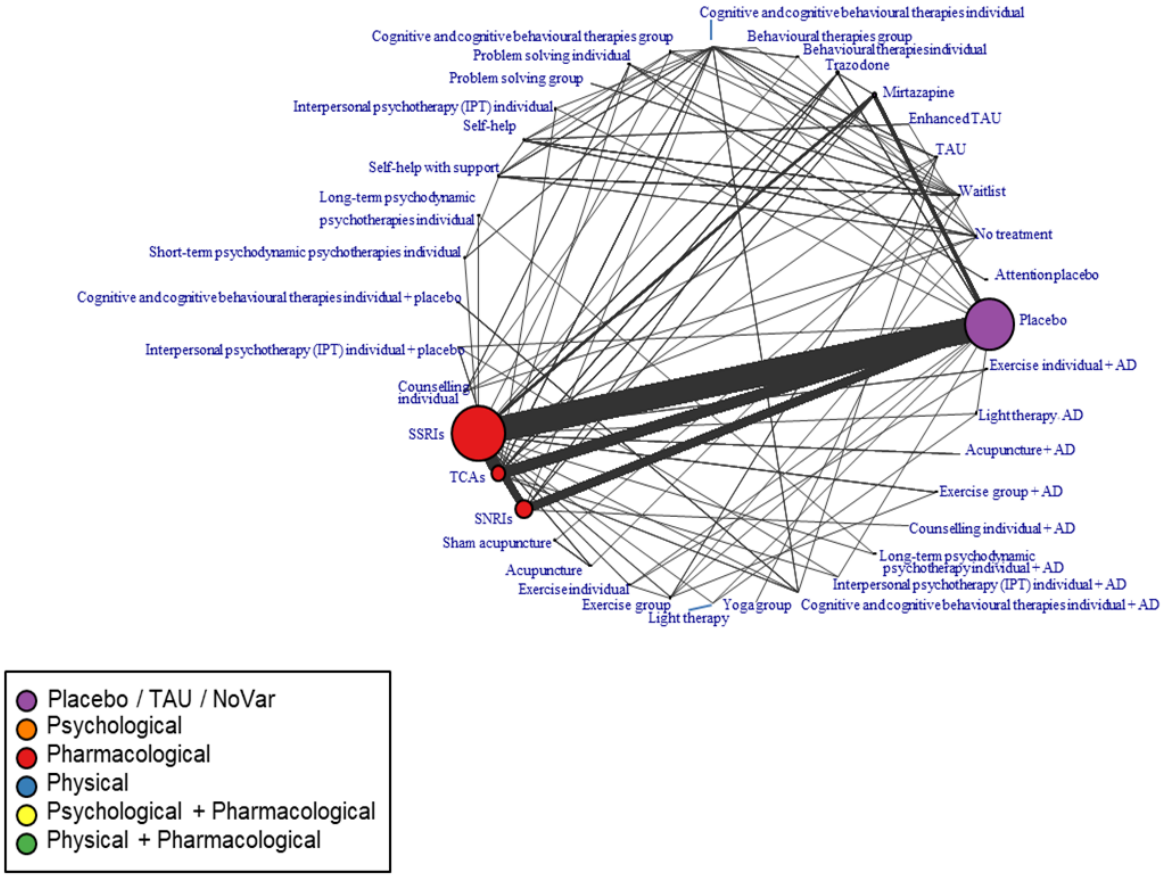
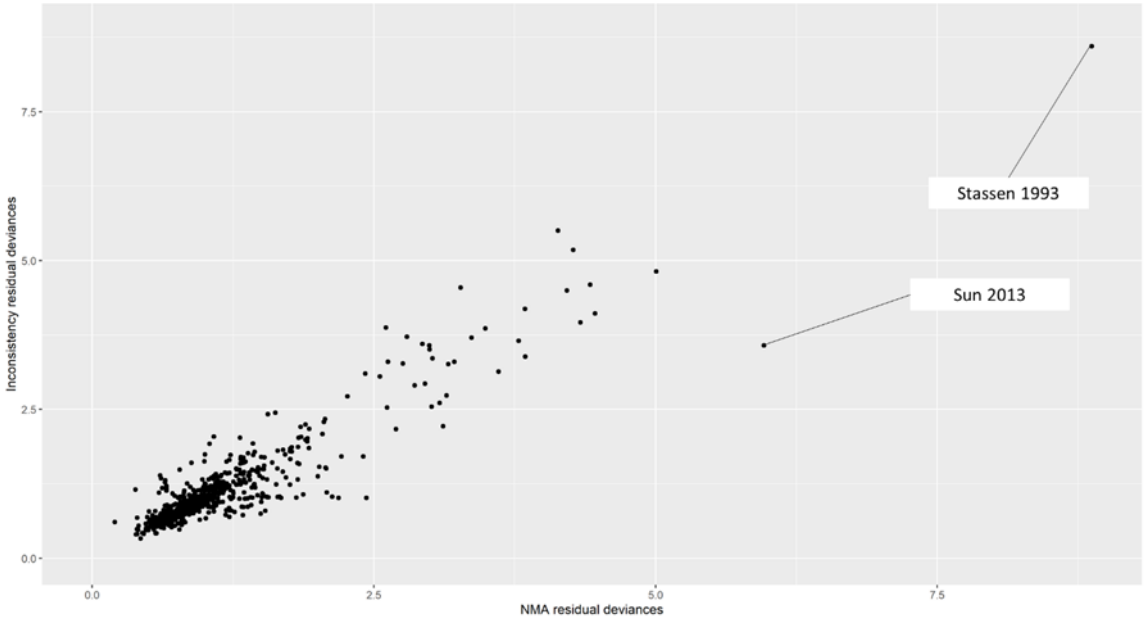


Figure 90. Deviance plot. Discontinuation (for any reason).



There is evidence of a decreased odds of discontinuation (lower OR corresponds to lower discontinuation) compared to Pill placebo for the following interventions (supplement B5, Figure 5.1 in appendix 5):

- Behavioural activation (BA) individual
- CBT individual (15 sessions or over)
- Enhanced TAU
- Escitalopram
- Fluoxetine
- No treatment
- Sertraline
- Waitlist

There was evidence of increased odds of discontinuation compared to Pill placebo for Trazodone.

The classes for which there is clear evidence suggesting a lower odds of discontinuation compared to Pill placebo are the following (supplement B5, Figure 5.2 in appendix 5):

- Enhanced TAU
- No treatment
- SSRIs
- Waitlist

The only class for which there was evidence of a higher odds of discontinuation compared to Pill placebo is Trazodone. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Enhanced TAU is the highest ranked class with a posterior median rank of 2nd (95% CrI 1st to 12th). The lowest ranked class is Trazodone 30th (95% CrI 23rd to 34th) (Excel file in supplement B6: *"Depression NMA more severe DISCONany bias-adjusted.xlsx"*, *"Ranks"* worksheet and Table 124).

Table 124. Posterior mean and median rank and 95% credible intervals by class. Discontinuation (for any reason).

Class	Posterior mean rank	Posterior median rank (95% CrI)
Enhanced TAU	2.7	2 (1, 12)
Waitlist	9.3	9 (3, 20)
Attention placebo	10.3	7 (1, 32)
Light therapy + AD	10.8	6 (1, 35)
Interpersonal psychotherapy (IPT) individual + AD	11.2	7 (1, 35)
Behavioural therapies individual	11.3	10 (2, 29)
Problem solving individual	11.4	10 (2, 30)
Interpersonal psychotherapy (IPT) individual	12.1	11 (2, 31)
TAU	12.1	11 (3, 27)
Self-help	12.2	10 (1, 34)
Sham acupuncture	12.3	10 (2, 32)
Long-term psychodynamic psychotherapies individual	14.8	13 (2, 33)
Cognitive and cognitive behavioural therapies individual	16.3	16 (6, 30)
Cognitive and cognitive behavioural therapies individual + AD	16.5	16 (3, 33)
Counselling individual	17.1	16 (4, 33)
Light therapy	17.9	17 (2, 36)

Acupuncture	18.3	17 (5, 34)
Cognitive and cognitive behavioural therapies group	19.5	19 (3, 35)
Yoga group	19.8	19 (2, 36)
Exercise individual	20.1	20 (3, 35)
Acupuncture + AD	21.1	21 (4, 35)
Exercise group + AD	21.7	22 (3, 36)
SSRIs	21.9	22 (15, 28)
Behavioural therapies group	21.9	22 (4, 36)
Exercise individual + AD	23.1	25 (3, 36)
Short-term psychodynamic psychotherapies individual	23.2	24 (6, 35)
Mirtazapine	23.9	24 (16, 31)
Placebo	24.5	25 (18, 30)
Counselling individual + AD	25	32 (1, 36)
Long-term psychodynamic psychotherapy individual + AD	25.1	29 (3, 36)
SNRIs	25.2	25 (18, 31)
Self-help with support	25.3	27 (7, 36)
TCAs	25.9	26 (18, 32)
Exercise group	26	29 (4, 36)
Problem solving group	26.6	33 (2, 36)
Trazodone	29.9	30 (23, 34)

Outcome: Discontinuation due to side effects

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who discontinued treatment. After excluding trials with zero events in all arms or with number events equal to the denominator in all arms, 278 trials of 22 interventions and 11 classes were included for this outcome (Table 125, Figure 91, Figure 92). 2 studies were excluded because they were disconnected from the network. A continuity correction was applied to data in 5 studies containing at least one zero cell to stabilize the results.

Although there was lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, the between-study heterogeneity was lower in the inconsistency model (supplement B5, Table 3.9 in appendix 3). However, the prediction of individual studies was similar in both models (Figure 93).

Reported results are therefore based on the random-effects NMA model, assuming consistency. Moderate between trials heterogeneity was observed relative to the size of the intervention effect estimates ($\tau_{study} = 0.44$ (95% CrI 0.33 to 0.55)). Pill placebo was used as the network reference treatment, and reported relative effects are presented compared to this (supplement B5, Figures 5.3 & 5.4 in appendix 5).

Table 125. Interventions, classes and number of patients (N) included in Discontinuation due to side effects analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	4231	Placebo	1	4231	
2	Mirtazapine	692	Mirtazapine	2	692	
3	Trazodone	365	Trazodone	3	365	

4	Interpersonal psychotherapy (IPT) individual + pill placebo	17	Interpersonal psychotherapy (IPT) individual + placebo	4	17	1
5	Citalopram	661	SSRIs	5	6445	1
6	Escitalopram	1108				
7	Fluoxetine	1831				
8	Paroxetine	2082				
9	Sertraline	763				
10	Amitriptyline	963	TCAs	6	2096	2
11	Clomipramine	174				
12	Imipramine	759				
13	Lofepramine	80				
14	Nortriptyline	120				
15	Duloxetine	1272	SNRIs	7	2478	1
16	Venlafaxine	1206				
17	Bright light therapy	4	Light therapy	8	4	Max(1,2)
18	Interpersonal psychotherapy (IPT) individual + nortriptyline	10	Interpersonal psychotherapy (IPT) individual + AD	9	10	Max(1,2)
19	Electroacupuncture + fluoxetine	2	Acupuncture + AD	10	14	Max(1,2)
20	Electroacupuncture + paroxetine	9				
21	Traditional acupuncture + paroxetine	3				
22	Bright light therapy + fluoxetine	2	Light therapy + AD	11	2	Max(1,2)

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 91. Network diagram of every study included in analysis by intervention. Discontinuation due to side effects

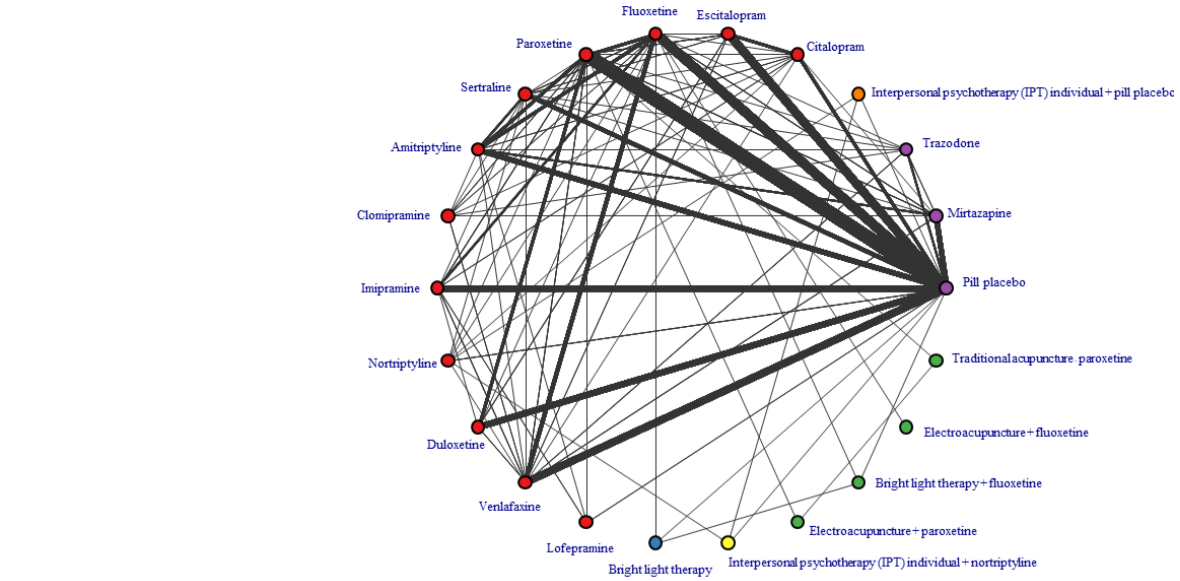


Figure 92. Network diagram of every study included in analysis by class. Discontinuation due to side effects.

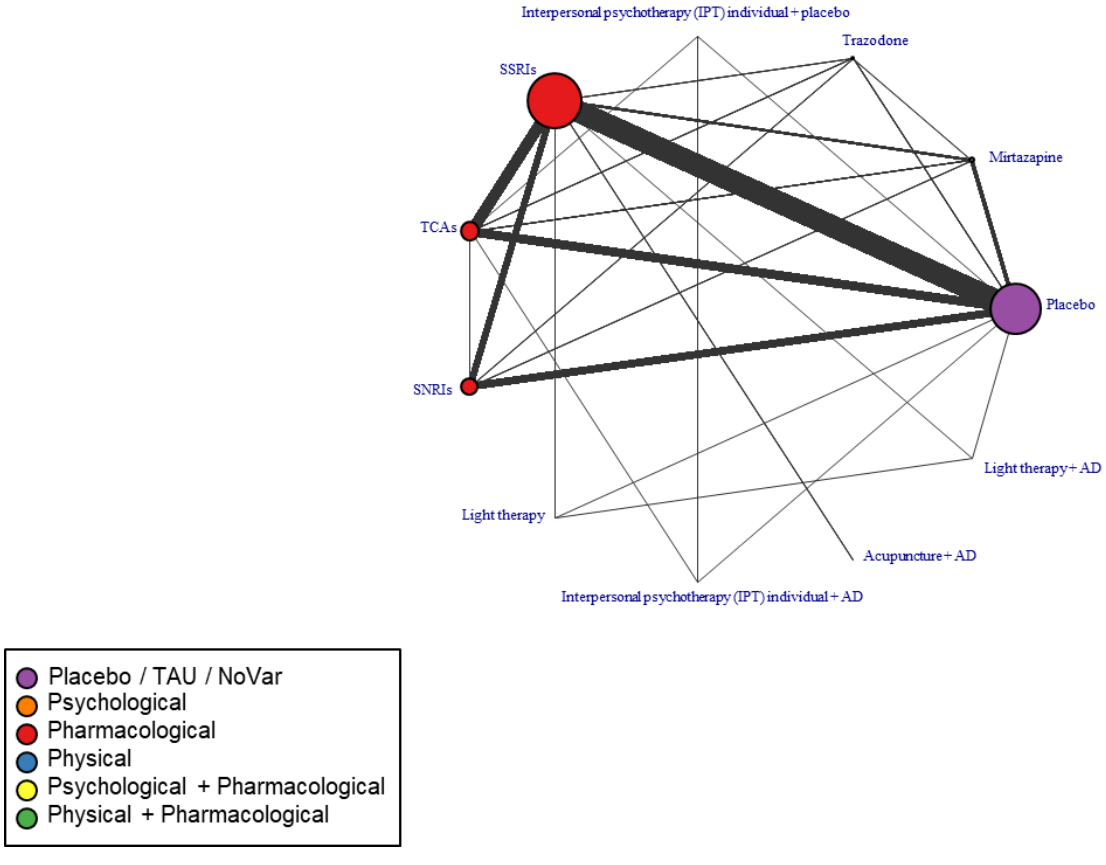
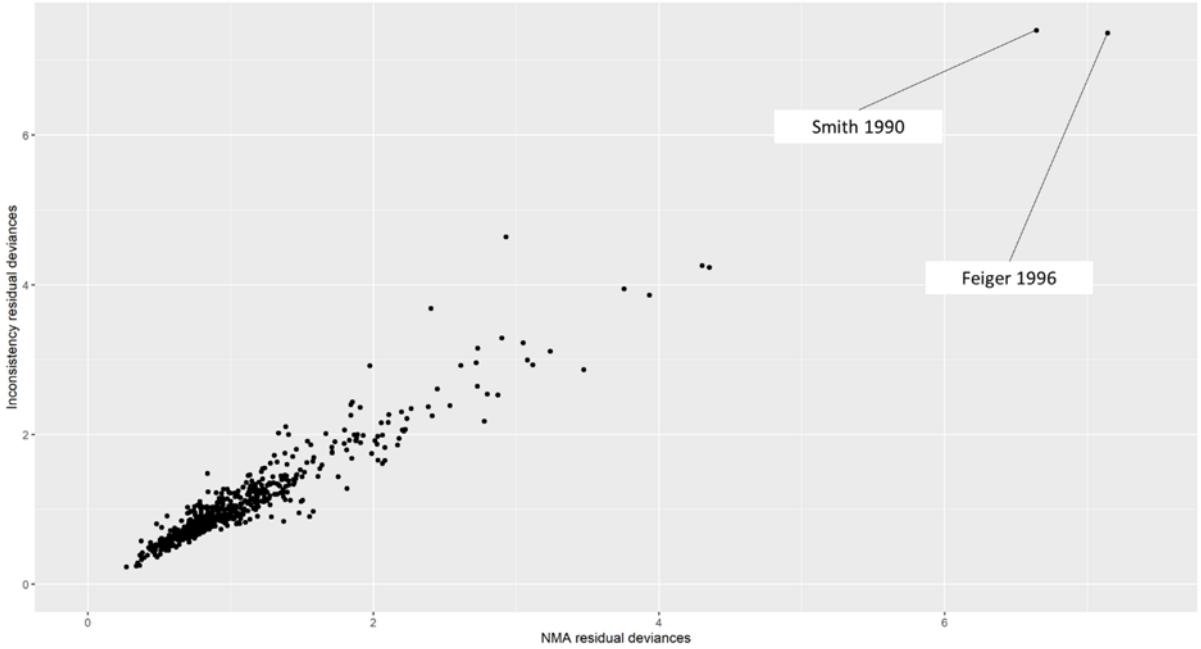


Figure 93. Deviance plot. Discontinuation due to side effects.



There is evidence suggesting that the following interventions have an increased odds of discontinuation due to SE compared to Pill placebo (supplement B5, Figure 5.3 in appendix 5):

- Clomipramine
- Duloxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Lofepramine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Sertraline
- Trazodone
- Venlafaxine

The classes for which there is evidence of having an increased odds in discontinuation due to SE are the following (supplement B5, Figure 5.4 in appendix 5):

- Mirtazapine
- Trazodone
- TCAs
- SSRIs

Placebo is the highest ranked class at 2nd (95% CrI 1st to 4th) (Table 126) and the highest ranked intervention at 2nd (95% CrI 1st to 5th) (Excel file in supplement B6: "*Depression NMA more severe DISCONse.xlsx*", "Ranks" worksheet). The lowest ranked intervention is Electroacupuncture + paroxetine with a posterior median rank of 18th (95% CrI 2nd to 20th). The lowest ranked class is TCAs with a posterior median rank of 9th (95% CrI 6th to 10th).

Table 126. Posterior mean and median rank and 95% credible intervals by class. Discontinuation due to side effects.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Placebo	2.2	2 (1, 4)
Light therapy	3.5	2 (1, 10)
Interpersonal psychotherapy (IPT) individual + AD	4.2	3 (1, 10)
SSRIs	4.6	5 (2, 7)
Mirtazapine	4.8	5 (2, 7)
Light therapy + AD	6.1	7 (1, 10)
Trazodone	6.3	6 (3, 9)
SNRIs	7.0	7 (4, 9)
Acupuncture + AD	7.9	9 (2, 10)
TCAs	8.4	9 (6, 10)

Outcome: Remission in completers

This analysis was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who completed treatment. 185 trials of 65 interventions and 35 classes were included in the analysis for this outcome (Table 127,

Figure 94, Figure 95). A continuity correction was added to data from 1 study (Sun 2010), and another study (Reynolds 1999a) was excluded because all participants in all arms experienced remission.

Although there was lower posterior mean residual deviance and DIC values in the NMA random effects consistency model, the between-study heterogeneity was lower in the inconsistency model (supplement B5, Table 3.10 in appendix 3). The prediction of individual studies was notably worse in one study (Rush 1977/Kovacs 1981), which investigated CBT individual (15 sessions or over) versus Impiramine (Figure 96).

Results are based on the random-effects NMA model, assuming consistency. Low between trial heterogeneity was observed for this outcome (τ_{study}=0.14 (95% CrI 0.02 to 0.24)). Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.5 & 5.6 in appendix 5).

Table 127. Interventions, classes and number of patients (N) included in Remission in completers analysis.

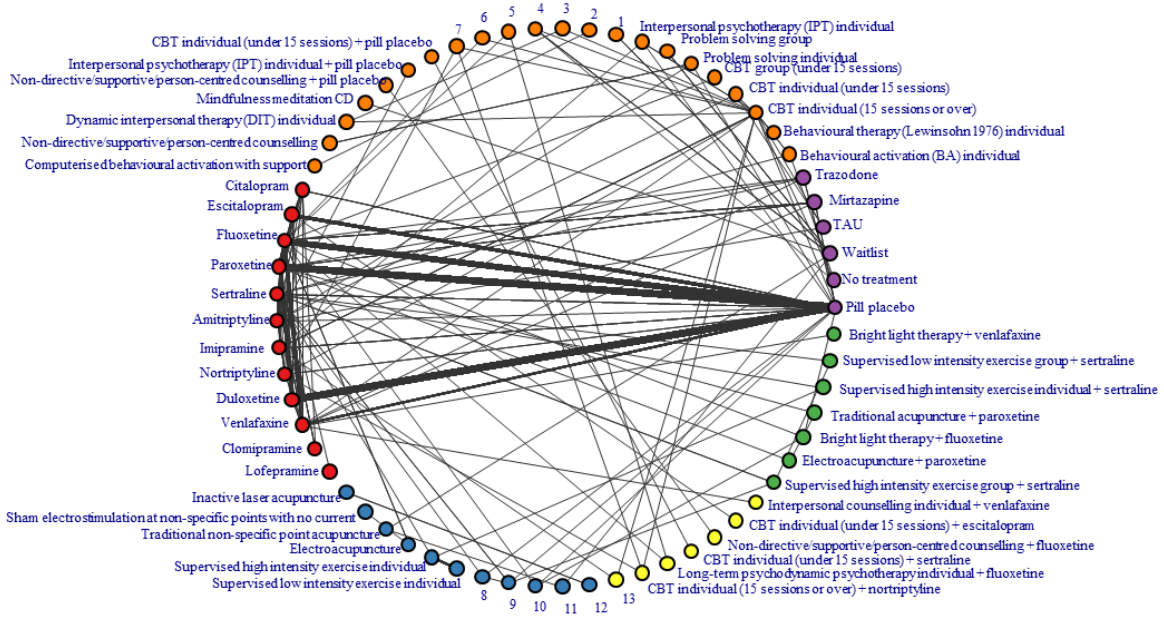
	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	5850	Placebo	1	5850	
2	No treatment	299	No treatment	2	299	
3	Waitlist	309	Waitlist	3	309	
4	TAU	45	TAU	4	45	
5	Mirtazapine	645	Mirtazapine	5	645	
6	Trazodone	552	Trazodone	6	552	
7	Behavioural activation (BA) individual	320	Behavioural therapies individual	7	330	1
8	Behavioural therapy (Lewinsohn 1976) individual	10				
9	CBT individual (15 sessions or over)	391	Cognitive and cognitive behavioural therapies individual	8	440	1
10	CBT individual (under 15 sessions)	49				
11	CBT group (under 15 sessions)	32	Cognitive and cognitive behavioural therapies group	9	32	1
12	Problem solving individual	191	Problem solving individual	10	191	1
13	Problem solving group	47	Problem solving group	11	47	1
14	Non-directive/supportive/person-centred counselling	103	Counselling individual	12	103	1
15	Interpersonal psychotherapy (IPT) individual	89	Interpersonal psychotherapy (IPT) individual	13	89	1
16	Cognitive bibliotherapy	147	Self-help	14	327	1
17	Mindfulness meditation CD	35				
18	Psychoeducational website	145				
19	Cognitive bibliotherapy with support	38	Self-help with support	15	323	1
20	Computerised-CBT (CCBT) with support	165				

21	Computerised behavioural activation with support	120				
22	Long-term psychodynamic psychotherapy individual	73	Long-term psychodynamic psychotherapies individual	16	73	1
23	Dynamic interpersonal therapy (DIT) individual	59	Short-term psychodynamic psychotherapies individual	17	101	1
24	Short-term psychodynamic psychotherapy individual	42				
25	CBT individual (15 sessions or over) + pill placebo	17	Cognitive and cognitive behavioural therapies individual + placebo	18	38	1
26	CBT individual (under 15 sessions) + pill placebo	21				
27	Interpersonal psychotherapy (IPT) individual + pill placebo	22	Interpersonal psychotherapy (IPT) individual + placebo	19	22	1
28	Non-directive/supportive/person-centred counselling + pill placebo	11	Counselling individual + placebo	20	11	1
29	Citalopram	1041	SSRIs	21	10361	2
30	Escitalopram	2457				
31	Fluoxetine	3001				
32	Paroxetine	3110				
33	Sertraline	752				
34	Amitriptyline	486	TCAs	22	1204	3
35	Clomipramine	135				
36	Imipramine	318				
37	Lofepramine	55				
38	Nortriptyline	210				
39	Duloxetine	3674	SNRIs	23	5949	2
40	Venlafaxine	2275				
41	Inactive laser acupuncture	33	Sham acupuncture	24	100	4
42	Sham electrostimulation at non-specific points with no current	22				
43	Traditional non-specific point acupuncture	45				
44	Electroacupuncture	67	Acupuncture	25	145	4
45	Laser acupuncture	36				
46	Traditional acupuncture	42				
47	Supervised high intensity exercise individual	109	Exercise individual	26	242	5
48	Supervised low intensity exercise individual	83				
49	Unsupervised high intensity exercise individual	50				
50	Supervised high intensity exercise group	80	Exercise group	27	80	1
51	Bright light therapy	28	Light therapy	28	28	4

52	CBT individual (15 sessions or over) + imipramine	16	Cognitive and cognitive behavioural therapies individual + AD	29	100	6
53	CBT individual (15 sessions or over) + nortriptyline	18				
54	CBT individual (under 15 sessions) + escitalopram	40				
55	CBT individual (under 15 sessions) + sertraline	26				
56	Long-term psychodynamic psychotherapy individual + fluoxetine	62	Long-term psychodynamic psychotherapy individual + AD	30	62	6
57	Interpersonal counselling individual + venlafaxine	11	Counselling individual + AD	31	24	6
58	Non-directive/supportive/person-centred counselling + fluoxetine	13				
59	Supervised high intensity exercise individual + sertraline	44	Exercise individual + AD	32	44	6
60	Supervised high intensity exercise group + sertraline	82	Exercise group + AD	33	114	6
61	Supervised low intensity exercise group + sertraline	32				
62	Electroacupuncture + paroxetine	49	Acupuncture + AD	34	100	4
63	Traditional acupuncture + paroxetine	51				
64	Bright light therapy + fluoxetine	27	Light therapy + AD	35	52	4
65	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 94. Network diagram of every study included in analysis by intervention. Remission in Completers.



1 Cognitive bibliotherapy; 2 Psychoeducational website; 3 Cognitive bibliotherapy with support; 4 Computerised CBT (CCBT) with support; 5 Long-term psychodynamic psychotherapy individual; 6 Short-term psychodynamic psychotherapy individual; 7 CBT individual (15 sessions or over) + pill placebo; 8 Unsupervised high intensity exercise individual; 9 Supervised high intensity exercise group; 10 Bright light therapy; 11 Traditional acupuncture; 12 Laser acupuncture; 13 CBT individual (15 sessions or over) + imipramine

Without the use of a class network the following treatments would be disconnected fro the rest of the network and would have to be excluded from the analysis: Psychoeducational website, CBT individual (under 15 sessions) + pill placebo, Non-directive/supportive/person-centred counselling + pill placebo, Inactive laser acupuncture, Computerised behavioural activation with support, CBT individual (under 15 sessions) + sertraline, Non-directive/supportive/person-centred counselling + fluoxetine, and Laser acupuncture

Figure 95. Network diagram of every study included in analysis by class. Remission in Completers.

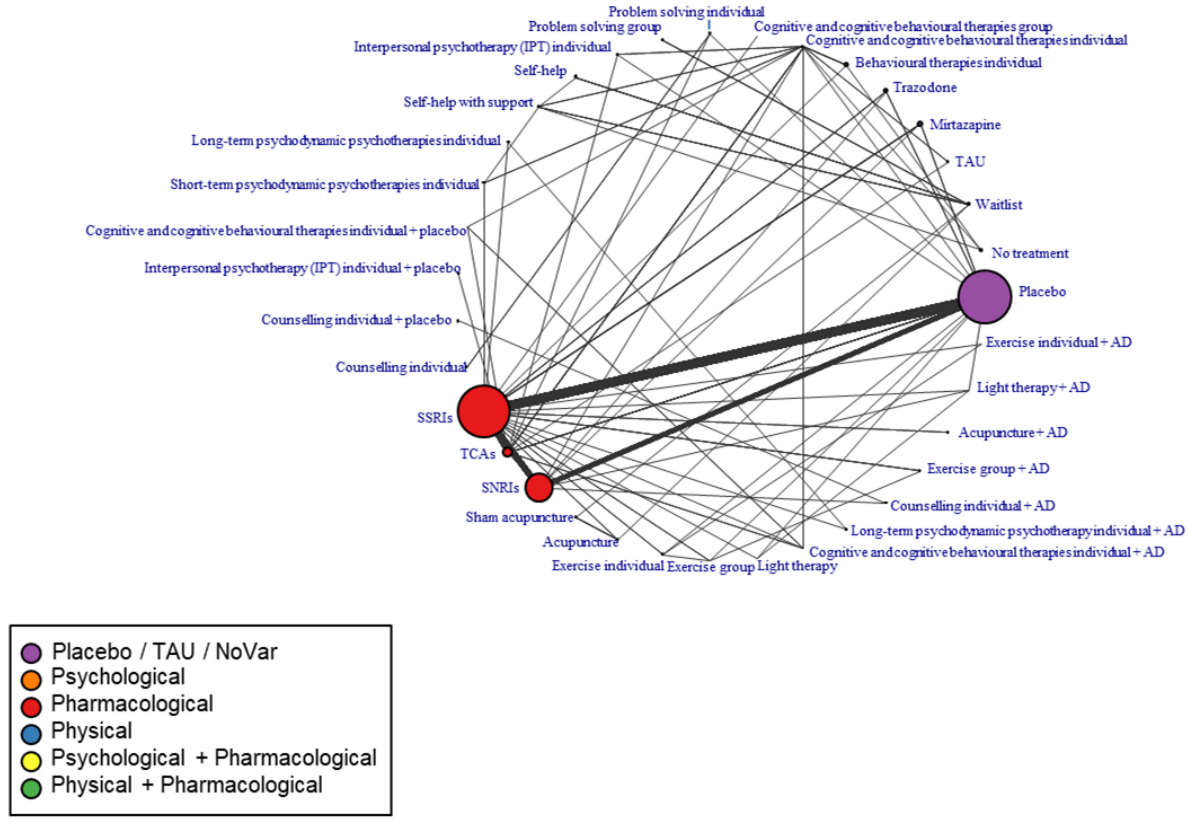
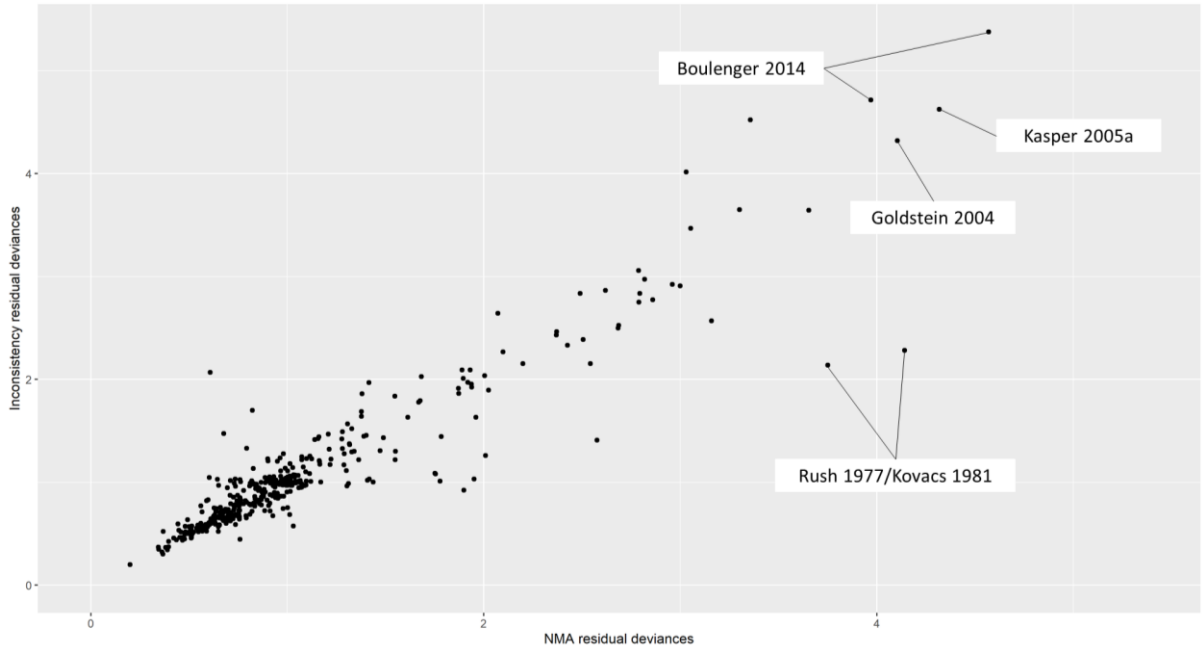


Figure 96. Deviance plot. Remission in Completers.



There is evidence suggesting the interventions with an increased odds of remission compared to Pill placebo are the following (supplement B5, Figure 5.5 in appendix 5):

- Amitriptyline

- Behavioural activation (BA) individual
- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + impiramine
- CBT individual (15 sessions or over) + nortriptyline
- CBT individual (15 sessions or over) + pill placebo
- CBT individual (under 15 sessions) + escitalopram
- CBT individual (under 15 sessions) + pill placebo
- Citalopram
- Clomipramine
- Cognitive bibliotherapy
- Computerised-CBT (CCBT) with support
- Duloxetine
- Dynamic interpersonal therapy (DIT) individual
- Electroacupuncture + paroxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Long-term psychodynamic psychotherapy individual
- Long-term psychodynamic psychotherapy individual + fluoxetine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Problem solving group
- Problem solving individual
- Sertraline
- Supervised high intensity exercise group
- Supervised high intensity exercise group + sertraline
- Supervised low intensity exercise group + sertraline
- Trazodone
- Venlafaxine

There is some evidence to suggest that Waitlist has a decreased odds of remission compared to Pill placebo.

The classes for which there is evidence of an increased odds of remission compared to Placebo are the following (supplement B5, Figure 5.6 in appendix 5):

- Cognitive and cognitive behavioural therapies individual + AD
- Cognitive and cognitive behavioural therapies individual + placebo
- Exercise group + AD
- Long-term psychodynamic psychotherapy individual
- Long-term psychodynamic psychotherapy individual + AD

- Mirtazapine
- SNRIs
- SSRIs
- TCAs
- Trazodone

For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Long-term psychodynamic psychotherapy individual + AD was the highest rank class at 1st (95% CrI 1st to 4th) (Table 128). The only intervention in this class, Long-term psychodynamic psychotherapy individual + fluoxetine, was the highest ranked intervention at 1st (95% CrI 1st to 3rd) (Excel file in supplement B6: *"Depression NMA more severe REMIScompleters.xlsx"*, *"Ranks"* worksheet). The lowest ranked class was Waitlist, with a posterior median rank of 30th (95% CrI 25th to 31st).

Table 128. Posterior mean and median rank and 95% credible intervals by class. Remission in Completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Long-term psychodynamic psychotherapy individual + AD	1.647	1 (1, 4)
Long-term psychodynamic psychotherapies individual	3.215	2 (1, 13)
Problem solving group	4.942	3 (1, 24)
Cognitive and cognitive behavioural therapies individual + AD	9.357	9 (4, 20)
Short-term psychodynamic psychotherapies individual	10.62	9 (3, 28)
Light therapy + AD	10.62	8 (3, 29)
Exercise group + AD	11.1	10 (4, 25)
Self-help	12.27	10 (3, 28)
Counselling individual + AD	13.42	11 (3, 30)
TCAs	13.67	13 (8, 22)
Problem solving individual	13.98	12 (2, 31)
Light therapy	14.32	12 (2, 31)
Interpersonal psychotherapy (IPT) individual	15.07	13 (3, 31)
Self-help with support	15.62	15 (4, 29)
SNRIs	16.06	16 (11, 21)
Acupuncture + AD	17.29	17 (4, 31)
Cognitive and cognitive behavioural therapies individual	17.55	17 (4, 30)
Acupuncture	17.55	17 (4, 30)
Behavioural therapies individual	17.66	18 (4, 31)
Exercise group	17.88	18 (3, 31)
Mirtazapine	18.43	18 (13, 24)
Trazodone	19.57	20 (14, 25)
SSRIs	20.21	20 (15, 25)
Counselling individual	20.22	23 (4, 31)
Cognitive and cognitive behavioural therapies group	20.64	23 (4, 31)
TAU	21.06	22 (10, 29)
Sham acupuncture	21.71	24 (5, 31)

Exercise individual + AD	22.28	24 (6, 31)
Exercise individual	22.92	24 (7, 31)
Placebo	25.54	26 (21, 29)
Waitlist	29.54	30 (25, 31)

Outcome: Remission in those randomised

A further analysis of remission was conducted using the NMA code given by Dias 2011 & 2013 for binomial data with the denominator being the total number of patients who were randomised. After excluding rials with zero events in all arms or with the number events equal to the denominator in all arms, 202 trials of 64 interventions and 38 classes were included in the analysis for this outcome (Table 129,

Figure 97, Figure 98).

No meaningful differences were observed in posterior mean residual deviance, though DIC was slightly lower in the random effects consistency model, and between-study heterogeneity slightly lower in the inconsistency model (supplement B5, Table 3.11 in appendix 3). The prediction of several individual studies was worse in the consistency model, suggesting some evidence of inconsistency. These studies investigated Behavioural activation (BA) individual, CBT individual (15 sessions or over), Sertraline, Impiramine and Venafalxine (Figure 99).

Reported results are based on the random-effects NMA model, assuming consistency. There was moderate between trial heterogeneity observed for this outcome $\left(\tau_{study} = 0.27\ (95\%\ \text{CrI}\ 0.20\ \text{to}\ 0.34)\right)$. Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.7 & 5.8 in appendix 5).

Table 129. Interventions, classes and number of patients (N) included in Remission in those randomised analysis.

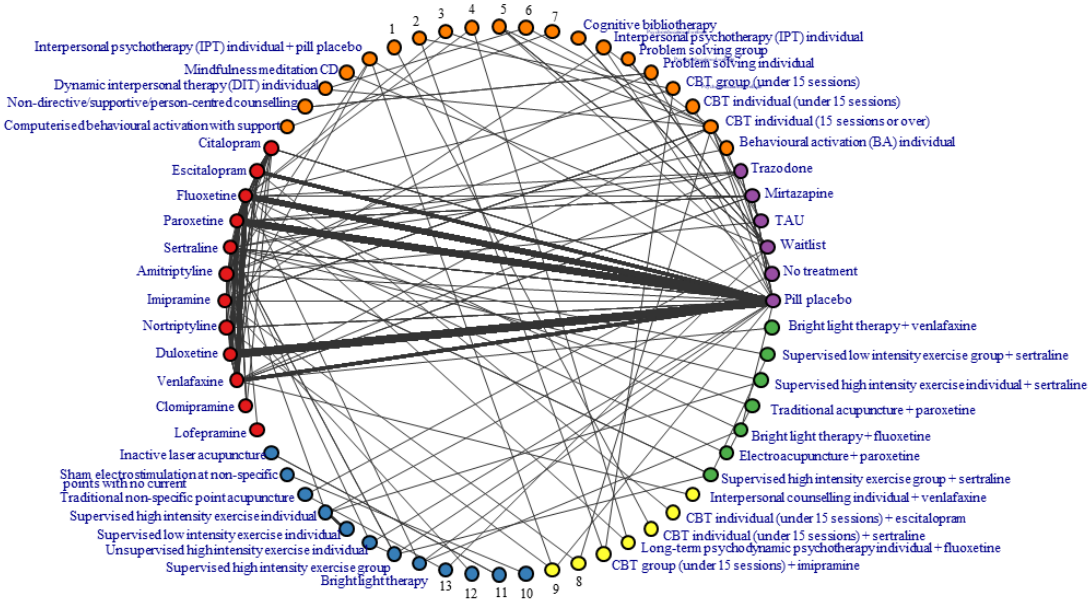
	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	8376	Placebo	1	8376	
2	No treatment	353	No treatment	2	353	
3	Waitlist	338	Waitlist	3	338	
4	TAU	60	TAU	4	60	
5	Mirtazapine	726	Mirtazapine	5	726	
6	Trazodone	742	Trazodone	6	742	
7	Behavioural activation (BA) individual	354	Behavioural therapies individual	7	354	1
8	CBT individual (15 sessions or over)	421	Cognitive and cognitive behavioural therapies individual	8	451	1
9	CBT individual (under 15 sessions)	30				
10	CBT group (under 15 sessions)	65	Cognitive and cognitive behavioural therapies group	9	65	1
11	Problem solving individual	232	Problem solving individual	10	232	1
12	Problem solving group	58	Problem solving group	11	58	1
13	Non-directive/supportive/person-centred counselling	124	Counselling individual	12	124	1
14	Interpersonal psychotherapy (IPT) individual	63	Interpersonal psychotherapy (IPT) individual	13	63	1
15	Cognitive bibliotherapy	156	Self-help	14	349	1
16	Mindfulness meditation CD	39				
17	Psychoeducational website	154				
18	Cognitive bibliotherapy with support	54	Self-help with support	15	416	1
19	Computerised-CBT (CCBT) with support	203				

20	Computerised behavioural activation with support	159				
21	Long-term psychodynamic psychotherapy individual	90	Long-term psychodynamic psychotherapies individual	16	90	1
22	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	17	129	1
23	Short-term psychodynamic psychotherapy individual	56				
24	Short-term psychodynamic psychotherapy group	24	Short-term psychodynamic psychotherapies group	18	24	1
25	CBT individual (under 15 sessions) + pill placebo	39	Cognitive and cognitive behavioural therapies individual + placebo	19	39	1
26	Interpersonal psychotherapy (IPT) individual + pill placebo	48	Interpersonal psychotherapy (IPT) individual + placebo	20	48	1
27	Citalopram	1676	SSRIs	21	15203	2
28	Escitalopram	3818				
29	Fluoxetine	3981				
30	Paroxetine	4571				
31	Sertraline	1157				
32	Amitriptyline	666	TCAs	22	1747	3
33	Clomipramine	184				
34	Imipramine	562				
35	Lofepramine	68				
36	Nortriptyline	267				
37	Duloxetine	5472	SNRIs	23	8727	2
38	Venlafaxine	3255				
39	Inactive laser acupuncture	36	Sham acupuncture	24	117	1
40	Sham electrostimulation at non-specific points with no current	29				
41	Traditional non-specific point acupuncture	52				
42	Electroacupuncture	28	Acupuncture	25	122	1
43	Laser acupuncture	41				
44	Traditional acupuncture	53				
45	Supervised high intensity exercise individual	177	Exercise individual	26	336	4
46	Supervised low intensity exercise individual	106				
47	Unsupervised high intensity exercise individual	53				
48	Supervised high intensity exercise group	104	Exercise group	27	104	1
49	Yoga group	15	Yoga group	28	15	1

50	Bright light therapy	32	Light therapy	29	32	1
51	CBT individual (15 sessions or over) + imipramine	25	Cognitive and cognitive behavioural therapies individual + AD	30	117	1
52	CBT individual (under 15 sessions) + escitalopram	52				
53	CBT individual (under 15 sessions) + sertraline	40				
54	CBT group (under 15 sessions) + imipramine	34	Cognitive and cognitive behavioural therapies group + AD	31	34	1
55	Long-term psychodynamic psychotherapy individual + fluoxetine	91	Long-term psychodynamic psychotherapy individual + AD	32	91	1
56	Interpersonal psychotherapy (IPT) individual + nortriptyline	16	Interpersonal psychotherapy (IPT) individual + AD	33	16	1
57	Interpersonal counselling individual + venlafaxine	13	Counselling individual + AD	34	13	1
58	Supervised high intensity exercise individual + sertraline	55	Exercise individual + AD	35	55	1
59	Supervised high intensity exercise group + sertraline	97	Exercise group + AD	36	134	1
60	Supervised low intensity exercise group + sertraline	37				
61	Electroacupuncture + paroxetine	58	Acupuncture + AD	37	112	1
62	Traditional acupuncture + paroxetine	54				
63	Bright light therapy + fluoxetine	29	Light therapy + AD	38	54	1
64	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 97. Network diagram of every study included in analysis by intervention. Remission in those randomised.



1 CBT individual (under 15 sessions) + pill placebo; 2 Short-term psychodynamic therapy group; 3 Short term psychodynamic psychotherapy individual; 4 Long-term psychodynamic psychotherapy individual; 5 Computerised CBT (CCBT) with support; 6 Cognitive bibliotherapy with support; 7 Psychoeducational website; 8 CBT individual (15 sessions or over) + imipramine; 9 Interpersonal psychotherapy (IPT) individual + nortriptyline; 10 Electroacupuncture; 11 Laser acupuncture; 12 Yoga therapy; 13 Traditional acupuncture

Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: Psychoeducational website, CBT individual (under 15 sessions) + pill placebo, Inactive laser acupuncture, Sham electrostimulation at non-specific points with no current, Computerised behavioural activation with support, CBT individual (under 15 sessions) + sertraline, Laser acupuncture, and Electroacupuncture

Figure 98. Network diagram of every study included in analysis by class. Remission in those randomised.

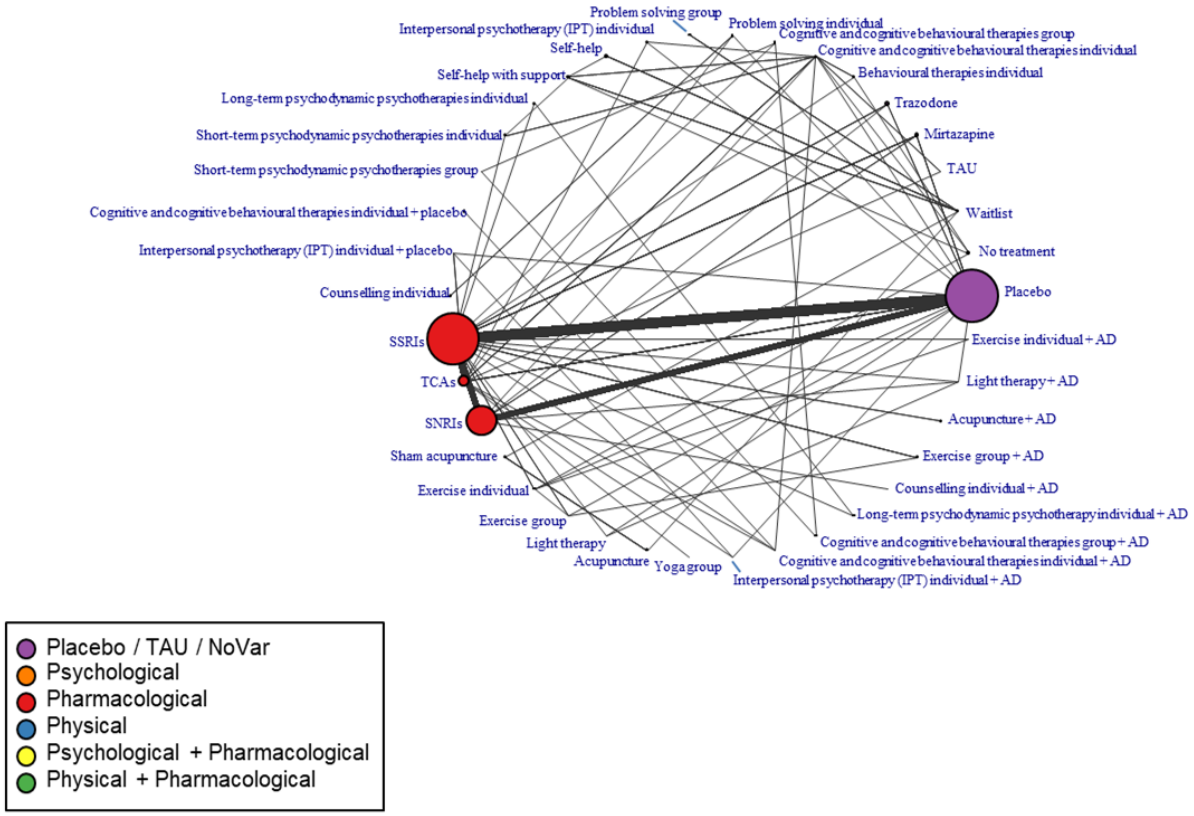
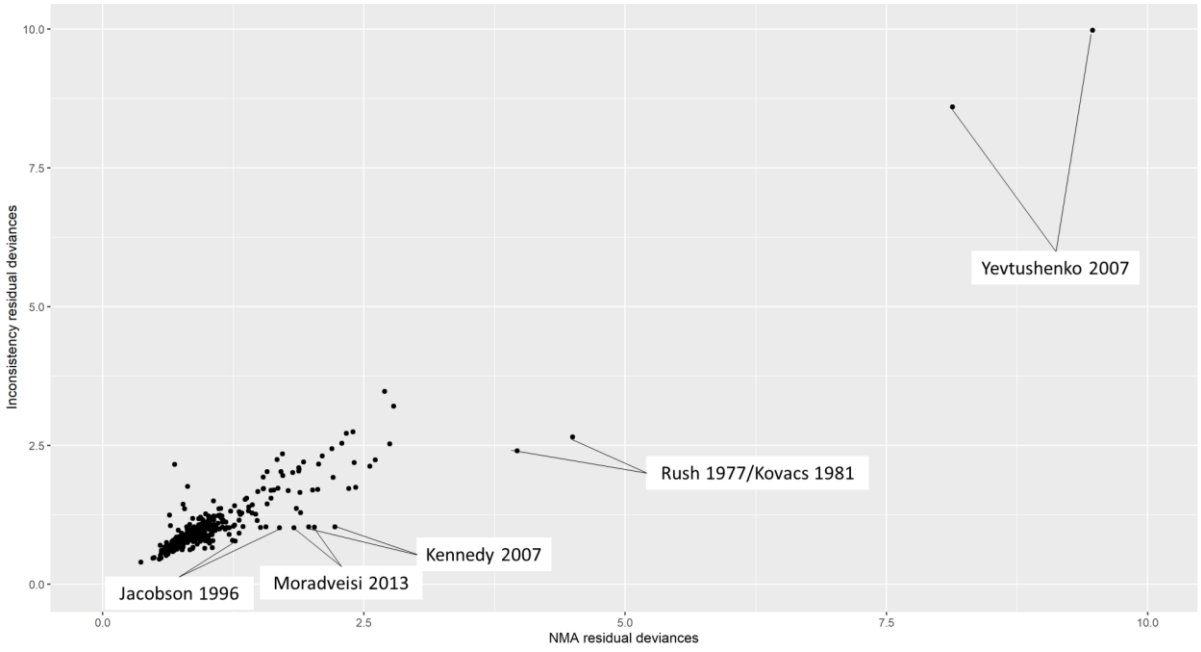


Figure 99. Deviance plot. Remission in those randomised.



There is evidence of increased odds of remission compared to Pill placebo for the following interventions (supplement B5, Figure 5.7 in appendix 5):

- Amitriptyline
- Behavioural activation (BA) individual

- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + impramine
- Citalopram
- Clomipramine
- Cognitive bibliography
- Duloxetine
- Dynamic interpersonal therapy (DIT) individual
- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Interpersonal psychotherapy (IPT) individual + nortriptyline
- Lofepramine
- Long-term psychodynamic psychotherapy individual
- Long-term psychodynamic psychotherapy individual + fluoxetine
- Mirtazapine
- Nortriptyline
- Paroxetine
- Problem solving group
- Problem solving individual
- Sertraline
- Supervised high intensity exercise group + sertraline
- Supervised low intensity exercise group + sertraline
- Trazodone
- Venlafaxine

Only one intervention, Short-term psychodynamic psychotherapy group, showed decreased odds of remission compared to Pill placebo.

The classes for which evidence suggests an increased odds of remission compared to Pill placebo are the following (supplement B5, Figure 5.8 in appendix 5):

- Long-term psychodynamic psychotherapy individual + AD
- Long-term psychodynamic psychotherapy individual
- Mirtazapine
- SNRIs
- SSRIs
- TCAs
- Trazodone

Short-term psychodynamic psychotherapy group, which contained only a single intervention of the same name, showed decreased odds of remission compared to Pill placebo. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Long-term psychodynamic psychotherapies individual was the highest ranked class at 2nd (95% CrI 1st to 17th) (Table 130). The highest ranked intervention, Long-term psychodynamic psychotherapy individual, was the only intervention in this class, with a posterior median rank of 2nd (95%CrI 1st to 9th) (Excel file in supplement B6: *"Depression NMA more severe REMISitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Short-term psychodynamic psychotherapies group at 35th (95% CrI 28th to 35th), and the lowest ranked intervention, also named Short-term psychodynamic psychotherapies group, was the only intervention in this class.

Table 130. Posterior mean and median rank and 95% credible intervals by class. Remission in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Long-term psychodynamic psychotherapies individual	3.87	2 (1, 17)
Long-term psychodynamic psychotherapy individual + AD	5.54	3 (1, 24)
Problem solving group	8.18	5 (1, 31)
Light therapy + AD	10.09	8 (2, 28)
Interpersonal psychotherapy (IPT) individual + AD	11	8 (1, 32)
Self-help	11.28	9 (2, 29)
Short-term psychodynamic psychotherapies individual	12.5	11 (2, 30)
Exercise group + AD	13.42	12 (3, 30)
Interpersonal psychotherapy (IPT) individual	13.48	11 (2, 32)
Behavioural therapies individual	13.84	12 (2, 32)
Problem solving individual	13.96	12 (2, 33)
Cognitive and cognitive behavioural therapies individual + AD	14.17	13 (3, 31)
Light therapy	14.77	12 (2, 33)
Counselling individual + AD	16.43	14 (1, 34)
TCAs	17.28	17 (9, 27)
Acupuncture	18.64	18 (2, 33)
SNRIs	18.76	19 (12, 25)
Cognitive and cognitive behavioural therapies individual	18.84	18 (5, 32)
TAU	19.14	19 (8, 31)
Mirtazapine	19.15	19 (12, 26)
Acupuncture + AD	19.19	19 (4, 33)
Self-help with support	19.56	20 (5, 32)
Exercise group	20.59	22 (4, 34)
SSRIs	21.81	22 (16, 27)
Exercise individual + AD	22.13	24 (4, 34)
Cognitive and cognitive behavioural therapies group	22.3	25 (4, 34)
Counselling individual	22.35	25 (4, 34)
Yoga group	22.36	26 (3, 35)
Sham acupuncture	22.55	26 (4, 34)
Exercise individual	22.69	24 (6, 33)
Cognitive and cognitive behavioural therapies group + AD	22.9	26 (3, 34)
Trazodone	23.11	23 (16, 29)

Placebo	27.78	28 (23, 32)
Waitlist	32.01	33 (25, 35)
Short-term psychodynamic psychotherapies group	34.32	35 (28, 35)

Outcome: Response in completers

The response analysis was first carried out only in those who completed treatment, using WinBUGS code given in supplement B5, appendix 1. After excluding trials with zero events in all arms or with the number events equal to the denominator in all arms, 250 trials reported response. Out of the remaining studies in the dataset, 21 reported change from baseline in completers (but not response) and 56 reported baseline and final scores in completers (but not response or change from baseline). This meant that 327 trials of 87 interventions and 44 classes were included in the analysis for this outcome (Table 131,

Figure 100,

Figure 101).

Posterior mean residual deviances, DIC and between-study heterogeneity were all lower in the random-effects NMA consistency model than in the inconsistency model (supplement B5, Table 3.12 in appendix 3). Prediction of data points were largely similar in both models, although for one study (Moradveisi 2013) the fit was substantially poorer in the consistency model, due to one arm in which the number of responders was equal to the number of completers (Figure 102).

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The bias parameter for comparisons with active versus control or counselling interventions was estimated to be 0.86 (95%CrI 0.33, 1.42). This indicated that smaller studies were likely to be biased in favour of active interventions versus control or counselling interventions. The posterior mean residual deviance, DIC and between study heterogeneity were substantially reduced compared to the base-case consistency model (supplement B5, Table 3.12 in appendix 3). Reported results are therefore based on the bias-adjusted random-effects NMA model. Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ("*Depression NMA more severe RESPcompleters bias-adjusted.xlsx"* and *"Depression NMA more severe RESPcompleters base-case.xlsx"*, respectively).

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.60\ (95\%\ CrI\ 0.52\ to\ 0.68)$). Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.9 & 5.10 in appendix 5).

Table 131. Interventions, classes and number of patients (N) included in Response in completers analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	9333	Placebo	1	9333	
2	Attention placebo	25	Attention placebo	2	25	
3	No treatment	266	No treatment	3	266	
4	Waitlist	371	Waitlist	4	371	
5	TAU	64	TAU	5	64	
6	Mirtazapine	1845	Mirtazapine	6	1845	
7	Trazodone	1003	Trazodone	7	1003	
8	Behavioural activation (BA) individual	310	Behavioural therapies individual	8	320	1
9	Behavioural therapy (Lewinsohn 1976) individual	10				
10	CBT individual (15 sessions or over)	348	Cognitive and cognitive behavioural therapies individual	9	507	1
11	CBT individual (under 15 sessions)	141				
12	Third-wave cognitive therapy individual	18				
13	CBT group (under 15 sessions)	64	Cognitive and cognitive behavioural therapies group	10	64	1
14	Problem solving individual	123	Problem solving individual	11	123	1
15	Problem solving group	47	Problem solving group	12	47	1

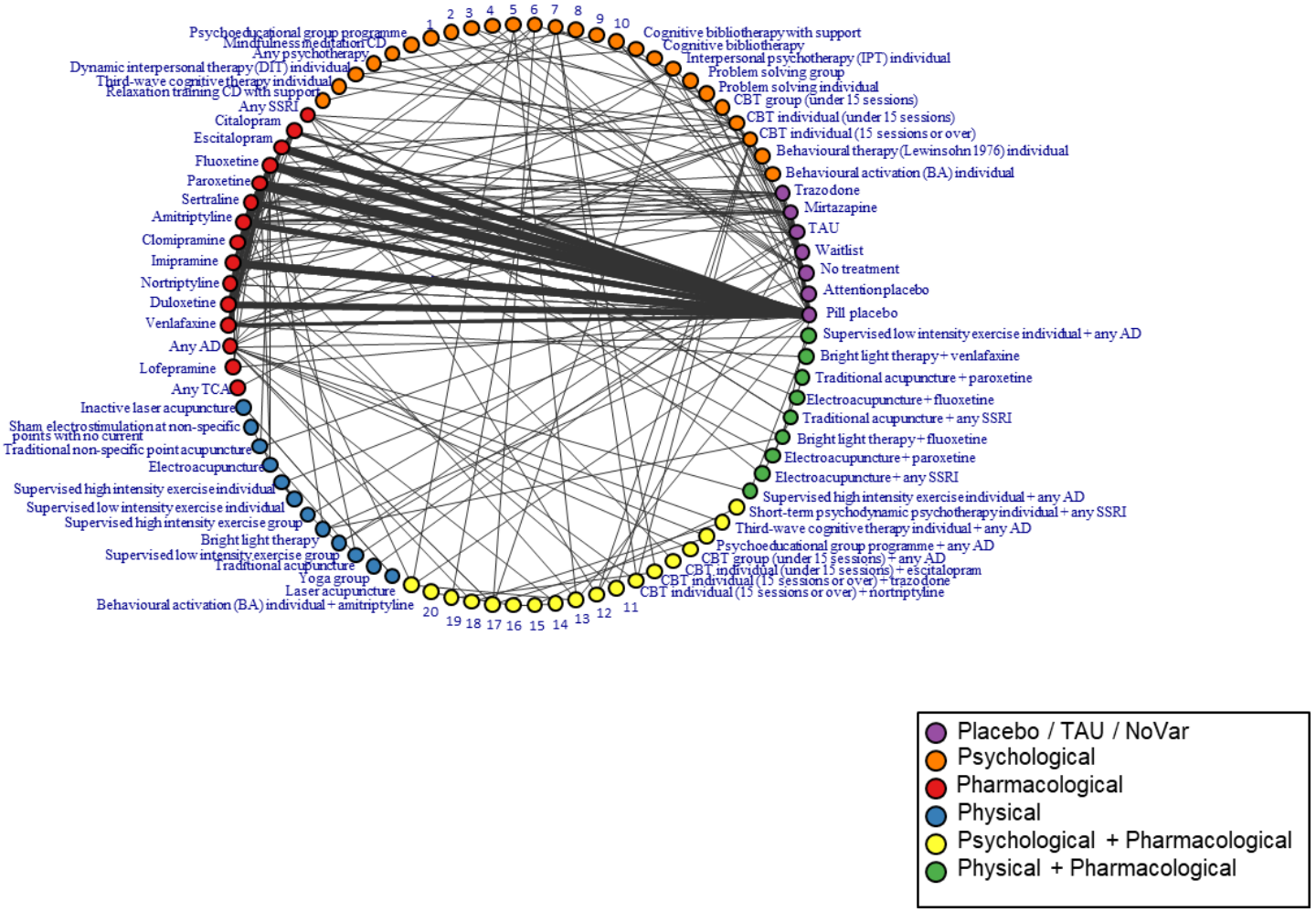
16	Non-directive/supportive/person-centred counselling	216	Counselling individual	13	216	1
17	Interpersonal psychotherapy (IPT) individual	132	Interpersonal psychotherapy (IPT) individual	14	132	1
18	Psychoeducational group programme	44	Psychoeducation group	15	44	1
19	Cognitive bibliotherapy	147	Self-help	16	231	2
20	Computerised-CBT (CCBT)	23				
21	Computerised attentional bias modification	26				
22	Mindfulness meditation CD	35				
23	Cognitive bibliotherapy with support	38	Self-help with support	17	189	3
24	Computerised-CBT (CCBT) with support	114				
25	Mindfulness meditation CD with support	19				
26	Relaxation training CD with support	18				
27	Dynamic interpersonal therapy (DIT) individual	59	Short-term psychodynamic psychotherapies individual	18	75	1
28	Short-term psychodynamic psychotherapy individual	16				
29	Music therapy group	12	Music therapy group	19	12	1
30	Any psychotherapy	27	Any psychotherapy	20	27	1
31	CBT individual (15 sessions or over) + pill placebo	26	Cognitive and cognitive behavioural therapies individual + placebo	21	26	1
32	Interpersonal psychotherapy (IPT) individual + pill placebo	69	Interpersonal psychotherapy (IPT) individual + placebo	22	69	1
33	Progressive muscle relaxation individual + pill placebo	11	Relaxation individual + placebo	23	11	1
34	Any SSRI	201	SSRIs	24	16720	4
35	Citalopram	1762				
36	Escitalopram	3396				
37	Fluoxetine	4804				
38	Paroxetine	4291				
39	Sertraline	2266				
40	Amitriptyline	2222	TCAs	25	4233	4
41	Any TCA	21				
42	Clomipramine	297				
43	Imipramine	1247				
44	Lofepramine	188				
45	Nortriptyline	258				
46	Duloxetine	3700	SNRIs	26	6569	4
47	Venlafaxine	2869				
48	Any AD	286	Any AD	27	286	4

49	Inactive laser acupuncture	33	Sham acupuncture	28	188	1
50	Sham electrostimulation at non-specific points with no current	22				
51	Traditional non-specific point acupuncture	133				
52	Electroacupuncture	83	Acupuncture	29	249	1
53	Laser acupuncture	36				
54	Traditional acupuncture	130				
55	Supervised high intensity exercise individual	47	Exercise individual	30	88	3
56	Supervised low intensity exercise individual	41				
57	Supervised high intensity exercise group	18	Exercise group	31	55	3
58	Supervised low intensity exercise group	37				
59	Yoga group	20	Yoga group	32	20	1
60	Bright light therapy	28	Light therapy	33	28	1
61	Behavioural activation (BA) individual + amitriptyline	12	Behavioural therapies individual + AD	34	22	5
62	Behavioural activation (BA) individual + any AD	10				
63	CBT individual (15 sessions or over) + amitriptyline	10	Cognitive and cognitive behavioural therapies individual + AD	35	157	5
64	CBT individual (15 sessions or over) + any AD	10				
65	CBT individual (15 sessions or over) + any SSRI	43				
66	CBT individual (15 sessions or over) + imipramine	16				
67	CBT individual (15 sessions or over) + nortriptyline	18				
68	CBT individual (15 sessions or over) + trazodone	10				
69	CBT individual (under 15 sessions) + escitalopram	40				
70	Third-wave cognitive therapy individual + any AD	10				
71	CBT group (under 15 sessions) + any AD	43	Cognitive and cognitive behavioural therapies group + AD	36	43	5
72	Interpersonal psychotherapy (IPT) individual + any AD	87	Interpersonal psychotherapy (IPT) individual + AD	37	87	5
73	Non-directive/supportive/person-centred counselling + any AD	55	Counselling individual + AD	38	71	5
74	Non-directive/supportive/person-centred counselling + any SSRI	16				

75	Short-term psychodynamic psychotherapy individual + any AD	152	Short-term psychodynamic psychotherapies individual + AD	39	168	5
76	Short-term psychodynamic psychotherapy individual + any SSRI	16				
77	Psychoeducational group programme + any AD	27	Psychoeducation group + AD	40	27	5
78	Progressive muscle relaxation individual + amitriptyline	10	Relaxation individual + AD	41	10	5
79	Supervised high intensity exercise individual + any AD	13	Exercise individual + AD	42	22	5
80	Supervised low intensity exercise individual + any AD	9				
81	Electroacupuncture + any SSRI	138	Acupuncture + AD	43	519	1
82	Electroacupuncture + fluoxetine	46				
83	Electroacupuncture + paroxetine	49				
84	Traditional acupuncture + any SSRI	185				
85	Traditional acupuncture + paroxetine	101				
86	Bright light therapy + fluoxetine	27	Light therapy + AD	44	52	1
87	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 100. Network diagram of every study included in analysis by intervention. Response in completers.



1 Non-directive/supportive/ person-centred counselling; 2 Music therapy group; 3 Computerised CBT (CCBT); 4 Computerised attentional bias modification; 5 Progressive muscle relaxation individual +pill placebo; 6 Interpersonal psychotherapy (IPT) individual +pill placebo; 7 CBT individual (15 sessions or over) + pill placebo; 8 Short-term psychodynamic psychotherapy individual; 9 Mindfulness meditation CD with support; 10 Computerised-CBT (CCBT) with support; 11 CBT individual (15 sessions or over) + imipramine; 12 CBT individual (15 sessions or over) + any SSRI; 13 Progressive muscle relaxation individual + amitriptyline; 14 Short-term psychodynamic psychotherapy individual + any AD; 15 Non-directive/supportive/ person-centred counselling + any SSRI; 16 Non-directive/supportive/ person-centred counselling + any AD; 17 Interpersonal psychotherapy (IPT) individual + any AD; 18 CBT individual (15 sessions or over) + any AD; 19 CBT individual (15 sessions or over) + amitriptyline; 20 Behavioural activation (BA) individual + any AD
Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: Attention placebo, Mindfulness meditation CD with support, Inactive laser acupuncture, Non-directive/supportive/person-centred counselling + any SSRI, Computerised attentional bias modification, Relaxation training CD with support, Laser acupuncture, and Short-term psychodynamic psychotherapy individual + any SSRI

Figure 101. Network diagram of every study included in analysis by class. Response in completers.

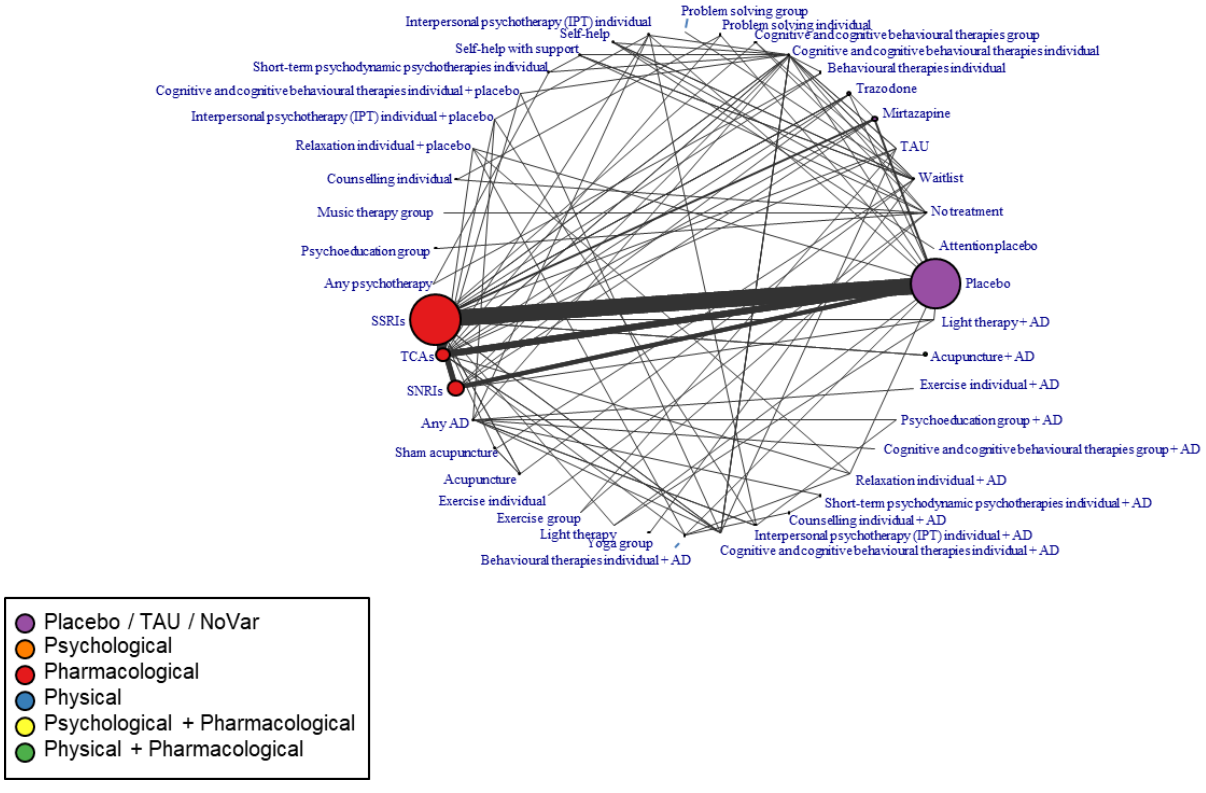
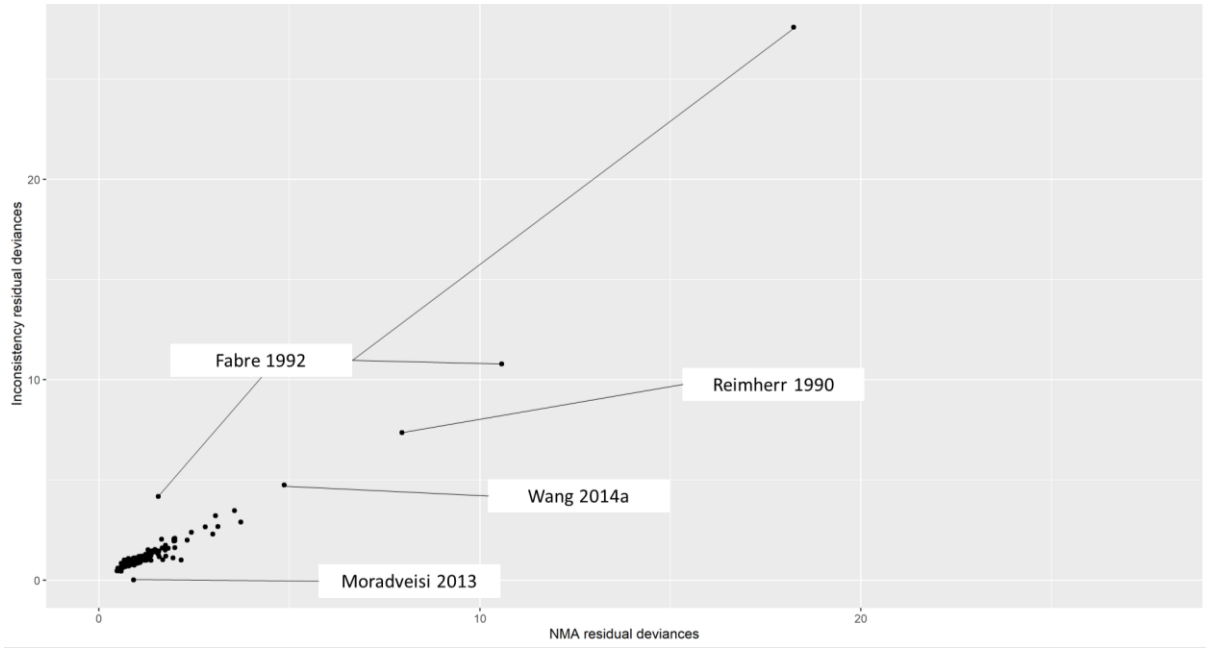


Figure 102. Deviance plot. Response in completers.



There is evidence suggesting the interventions with an increased odds of response compared to Pill placebo are the following (supplement B5, Figure 5.9 in appendix 5):

- Amitriptyline
- Any SSRI
- Any TCA

- Behavioural therapy (Lewinsohn 1976) individual
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + amitriptyline
- CBT individual (15 sessions or over) + any AD
- CBT individual (15 sessions or over) + any SSRI
- CBT individual (15 sessions or over) + impramine
- CBT individual (15 sessions or over) + nortriptyline
- CBT individual (15 sessions or over) + trazodone
- CBT individual (under 15 sessions)
- CBT individual (under 15 sessions) + escitalopram
- Citalopram
- Clomipramine
- Cognitive bibliography
- Duloxetine
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Electroacupuncture + paroxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Lofepramine
- Mirtazapine
- Non-directive/supportive/person-centred counselling
- Nortriptyline
- Paroxetine
- Problem solving group
- Problem solving individual
- Sertraline
- Third-wave cognitive therapy individual + any AD
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Trazodone
- Venlafaxine

There is evidence to suggest Waitlist has a decreased odds of response compared to Pill placebo.

The classes for which there is evidence of an increased odds of response compared to Pill placebo are the following (supplement B5, Figure 5.10 in appendix 5):

- Acupuncture + AD
- Cognitive and cognitive behavioural therapies individual + AD
- Mirtazapine
- Problem solving group

- SNRIs
- SSRIs
- TCAs
- Trazodone

Waitlist is the only class for which there is evidence of decreased odds of response compared to Pill placebo. For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Problem solving group is the highest ranked class at 2nd (95% CrI 1st to 17th), though Acupuncture + AD (6th; 95% CrI 2nd to 15th) and Cognitive and cognitive behavioural therapies individual + AD (7th; 95% CrI 2nd to 15th) also rank highly (Table 132). The highest ranked intervention is Traditional acupuncture + any SSRI, with a posterior median rank of 3rd (95% CrI 1st to 10th) (Excel file in supplement B6: *"Depression NMA more severe RESPcompleters bias-adjusted.xlsx"*, *"Ranks"* worksheet). The lowest ranked class is Waitlist, with a posterior median rank of 36th (95% CrI 30th to 38th). The lowest ranked active class is Counselling individual + AD with a posterior median rank of 33rd (95% CrI 6th to 38th).

Table 132. Posterior mean and median rank and 95% credible intervals by class. Response in completers.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Problem solving group	3.8	2 (1, 17)
Acupuncture + AD	6.4	6 (2, 15)
Cognitive and cognitive behavioural therapies individual + AD	7.2	7 (2, 15)
Exercise individual + AD	9.3	5 (1, 34)
Problem solving individual	11.2	9 (1, 33)
Light therapy + AD	12	10 (2, 31)
Yoga group	12.1	9 (1, 35)
Psychoeducation group	14.2	12 (1, 35)
Behavioural therapies individual	14.3	13 (3, 32)
Cognitive and cognitive behavioural therapies group + AD	15.3	13 (1, 36)
Short-term psychodynamic psychotherapies individual	15.9	14 (2, 35)
Counselling individual	15.9	14 (2, 36)
Exercise group	17.6	16 (2, 36)
Cognitive and cognitive behavioural therapies individual	17.7	17 (6, 32)
Exercise individual	18	16 (1, 38)
TAU	18	17 (8, 31)
TCAs	19.3	19 (13, 26)
Light therapy	19.7	19 (3, 37)
SNRIs	19.8	20 (13, 27)
Relaxation individual + AD	19.9	19 (1, 38)
Self-help	20.1	20 (2, 37)
Interpersonal psychotherapy (IPT) individual + AD	20.6	21 (3, 37)
Mirtazapine	20.8	21 (13, 28)
Behavioural therapies individual + AD	22.5	25 (3, 38)
Cognitive and cognitive behavioural therapies group	23	25 (4, 37)

SSRIs	23.1	23 (16, 29)
Attention placebo	23.3	28 (1, 38)
Acupuncture	23.7	25 (8, 36)
Interpersonal psychotherapy (IPT) individual	23.7	25 (5, 37)
Music therapy group	24.2	27 (3, 38)
Trazodone	24.8	25 (17, 32)
Short-term psychodynamic psychotherapies individual + AD	25.3	29 (4, 38)
Psychoeducation group + AD	25.6	28 (4, 38)
Self-help with support	28	30 (9, 38)
Counselling individual + AD	29.3	33 (6, 38)
Placebo	29.9	30 (24, 35)
Sham acupuncture	30.1	32 (13, 38)
Waitlist	35.4	36 (30, 38)

Outcome: Response in those randomised

A further response analysis was first carried out only in all patients who were randomised, using WinBUGS code given in supplement B5, appendix 1. After excluding trials with zero events or with the number events equal to the denominator in all arms, 280 trials reported response. Out of the remaining studies, 31 reported change from baseline in completers (but not response) and 53 reported baseline and final scores in completers (but not response or change from baseline). This meant that 364 trials of 83 interventions and 43 classes were included in the analysis for this outcome (Table 133,

Figure 103, Figure 104).

Lower posterior mean residual deviance and between study heterogeneity in the inconsistency model suggested evidence of inconsistency (supplement B5, Table 3.13 in appendix 3). The inconsistency model notably predicted the data in one study (Sahranavard 2018) much better than the consistency model, further adding evidence of inconsistency (Figure 105). This study compared Waitlist, Dialectical behavioural therapy (DBT) individual and CBT group (under 15 sessions).

Reported results are based on the random-effects NMA model, assuming consistency but should be interpreted with caution due to the identification of potential inconsistency. Relative to the size of the intervention effect estimates, moderate between trial heterogeneity was observed for this outcome $\left(\tau_{study} = 0.26\ (95\%\ \text{CrI}\ 0.21\ \text{to}\ 0.31)\right)$. Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.11 & 5.12 in appendix 5).

Table 133. Interventions, classes and number of patients (N) included in Response in those randomised analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	15384	Placebo	1	15384	
2	Attention placebo	36	Attention placebo	2	36	
3	No treatment	441	No treatment	3	441	
4	Waitlist	349	Waitlist	4	349	
5	TAU	176	TAU	5	176	
6	Mirtazapine	2629	Mirtazapine	6	2629	
7	Trazodone	1181	Trazodone	7	1181	
8	Behavioural activation (BA) individual	368	Behavioural therapies individual	8	368	1
9	CBT individual (15 sessions or over)	470	Cognitive and cognitive behavioural therapies individual	9	779	1
10	CBT individual (under 15 sessions)	260				
11	Dialectical behavioural therapy (DBT) individual	10				
12	Third-wave cognitive therapy individual	39				
13	CBT group (under 15 sessions)	155	Cognitive and cognitive behavioural therapies group	10	155	1
14	Problem solving individual	338	Problem solving individual	11	338	1
15	Non-directive/supportive/person-centred counselling	421	Counselling individual	12	421	1
16	Interpersonal psychotherapy (IPT) individual	61	Interpersonal psychotherapy (IPT) individual	13	61	1
17	Cognitive bibliotherapy	32	Self-help	14	168	2
18	Computerised-CBT (CCBT)	97				
19	Mindfulness meditation CD	39				
20	Cognitive bibliotherapy with support	66	Self-help with support	15	274	1

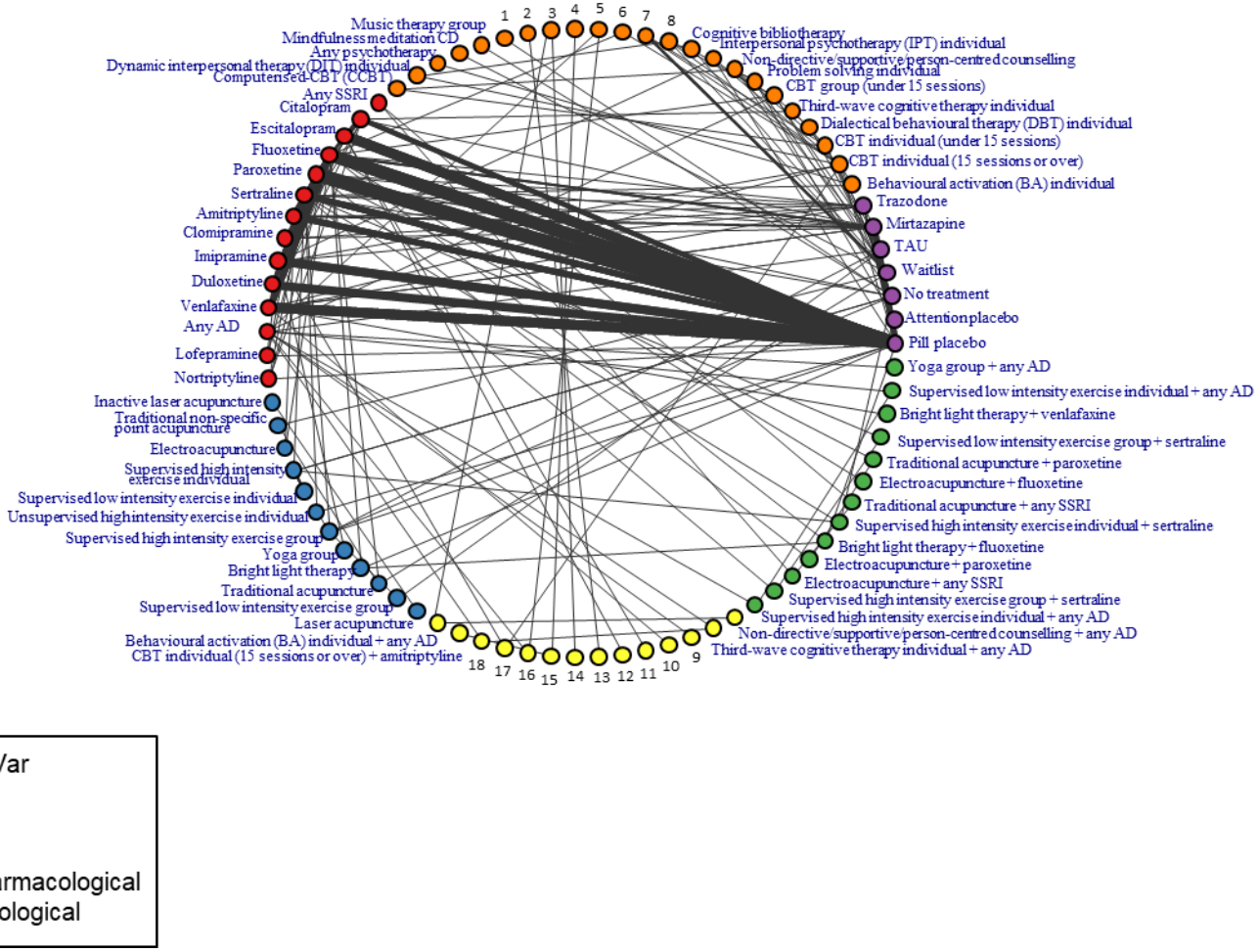
21	Computerised-CBT (CCBT) with support	208				
22	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	16	217	1
23	Short-term psychodynamic psychotherapy individual	144				
24	Music therapy group	12	Music therapy group	17	12	1
25	Mindfulness-based cognitive therapy (MBCT) group	15	Mindfulness or meditation group	18	15	1
26	Peer support group	39	Peer support group	19	39	1
27	Any psychotherapy	22	Any psychotherapy	20	22	1
28	CBT individual (15 sessions or over) + pill placebo	14	Cognitive and cognitive behavioural therapies individual + placebo	21	58	1
29	CBT individual (under 15 sessions) + pill placebo	44				
30	Non-directive/supportive/person-centred counselling + pill placebo	26	Counselling individual + placebo	22	26	1
31	Any SSRI	156	SSRIs	23	26961	3
32	Citalopram	3242				
33	Escitalopram	5863				
34	Fluoxetine	7732				
35	Paroxetine	6661				
36	Sertraline	3307				
37	Amitriptyline	2519	TCAs	24	5437	4
38	Clomipramine	414				
39	Imipramine	2061				
40	Lofepramine	242				
41	Nortriptyline	201				
42	Duloxetine	5472	SNRIs	25	10469	3
43	Venlafaxine	4997				
44	Any AD	188	Any AD	26	188	5
45	Inactive laser acupuncture	22	Sham acupuncture	27	74	6
46	Traditional non-specific point acupuncture	52				
47	Electroacupuncture	77	Acupuncture	28	217	6
48	Laser acupuncture	25				
49	Traditional acupuncture	115				
50	Supervised high intensity exercise individual	114	Exercise individual	29	273	7
51	Supervised low intensity exercise individual	106				
52	Unsupervised high intensity exercise individual	53				
53	Supervised high intensity exercise group	106	Exercise group	30	126	1

54	Supervised low intensity exercise group	20				
55	Yoga group	45	Yoga group	31	45	1
56	Bright light therapy	32	Light therapy	32	32	6
57	Behavioural activation (BA) individual + any AD	10	Behavioural therapies individual + AD	33	10	8
58	CBT individual (15 sessions or over) + amitriptyline	12	Cognitive and cognitive behavioural therapies individual + AD	34	158	8
59	CBT individual (15 sessions or over) + any AD	10				
60	CBT individual (15 sessions or over) + imipramine	25				
61	CBT individual (15 sessions or over) + trazodone	11				
62	CBT individual (under 15 sessions) + escitalopram	52				
63	CBT individual (under 15 sessions) + sertraline	38				
64	Third-wave cognitive therapy individual + any AD	10				
65	CBT group (under 15 sessions) + any AD	20	Cognitive and cognitive behavioural therapies group + AD	35	20	8
66	Interpersonal counselling individual + venlafaxine	12	Counselling individual + AD	36	52	8
67	Non-directive/supportive/person-centred counselling + any AD	15				
68	Non-directive/supportive/person-centred counselling + fluoxetine	25				
69	Cognitive bibliotherapy + escitalopram	79	Self-help + AD	37	79	8
70	Peer support group + any AD	42	Peer support group + AD	38	42	8
71	Supervised high intensity exercise individual + any AD	14	Exercise individual + AD	39	40	8
72	Supervised high intensity exercise individual + sertraline	15				
73	Supervised low intensity exercise individual + any AD	11				
74	Supervised high intensity exercise group + sertraline	42	Exercise group + AD	40	79	8
75	Supervised low intensity exercise group + sertraline	37				
76	Yoga group + any AD	15	Yoga group + AD	41	15	8
77	Electroacupuncture + any SSRI	160	Acupuncture + AD	42	553	9
78	Electroacupuncture + fluoxetine	48				
79	Electroacupuncture + paroxetine	80				

80	Traditional acupuncture + any SSRI	161				
81	Traditional acupuncture + paroxetine	104				
82	Bright light therapy + fluoxetine	29	Light therapy + AD	43	54	6
83	Bright light therapy + venlafaxine	25				

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 103. Network diagram of every study included in analysis by intervention. Response in those randomised.



1 Minfulness-based cognitive therapy (MBCT) group; 2 Non-directive/supportive/person-centred counselling + pill placebo; 3 CBT individual (under 15 sessions) + pill placebo; 4 CBT individual (15 sessions or over) + pill placebo; 5 Peer support; 6 Short-term psychodynamic therapy individual; 7 Computerised-CBT (CCBT) with support; 8 Cognitive

bibliotherapy with support; 9 CBT group (under 15 sessions) + any AD; 10 Interpersonal counselling individual + venlafaxine; 11 Cognitive bibliotherapy + escitalopram; 12 CBT individual (under 15 sessions) + citalopram; 13 Non-directive/supportive/person-centred counselling + fluoxetine; 14 CBT individual (under 15 sessions) + sertraline; 15 Peer support group + any AD; 16 CBT individual (15 sessions or over) + trazodone; 17 CBT individual (15 sessions or over) + imipramine; 18 CBT individual (15 sessions or over) + any AD

Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: CBT individual (15 sessions or over) + pill placebo, CBT individual (under 15 sessions) + pill placebo, Non-directive/supportive/person-centred counselling + pill placebo, Any SSRI, Inactive laser acupuncture, Behavioural activation (BA) individual + any AD, CBT individual (15 sessions or over) + amitriptyline, Electroacupuncture + any SSRI, CBT individual (15 sessions or over) + trazodone, CBT individual (under 15 sessions) + sertraline, Non-directive/supportive/person-centred counselling + fluoxetine, Traditional acupuncture + any SSRI, Laser acupuncture, and Non-directive/supportive/person-centred counselling + any AD

Figure 104. Network diagram of every study included in analysis by class. Response in those randomised.

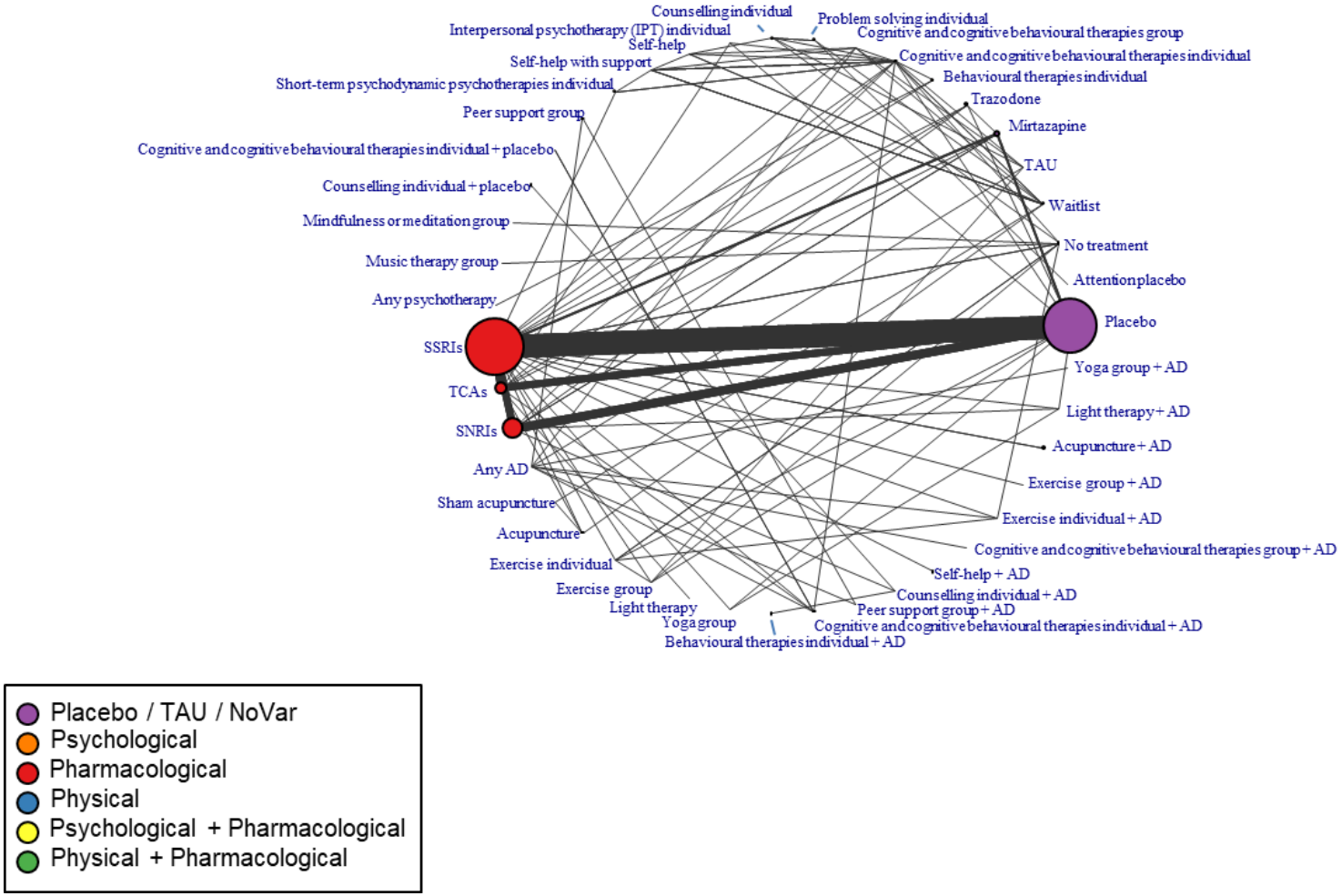
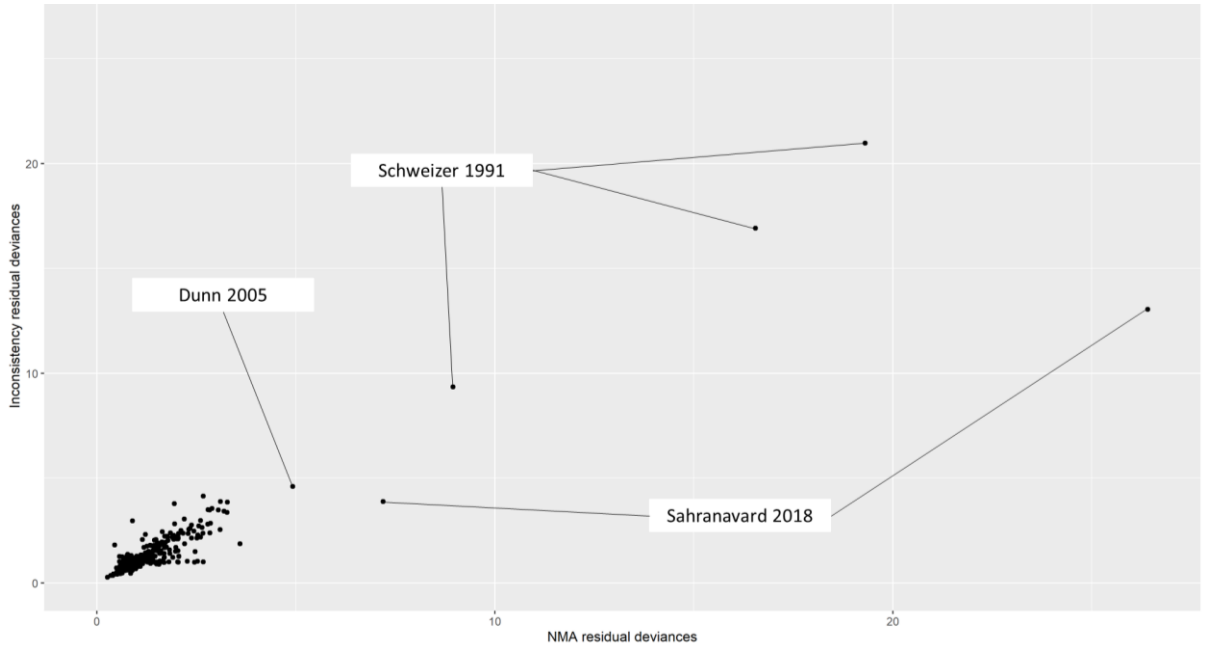


Figure 105. Deviance plot. Response in those randomised.



Interventions for which evidence suggests an increased odds of response compared to Pill placebo are the following (supplement B5, Figure 5.11 in appendix 5):

- Amitriptyline
- Any AD
- Any SSRI
- Behavioural activation (BA) individual
- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT group (under 15 sessions)
- CBT group (under 15 sessions) + any AD
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + any AD
- CBT individual (15 sessions or over) + imipramine
- CBT individual (15 sessions or over) + trazodone
- CBT individual (under 15 sessions)
- Citalopram
- Clomipramine
- Cognitive bibliotherapy
- Cognitive bibliotherapy with support
- Computerised-CBT (CCBT)
- Computerised-CBT (CCBT) with support
- Dynamic interpersonal therapy (DIT) individual
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Electroacupuncture + paroxetine

- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Lofepramine
- Mindfulness medication CD
- Mindfulness-based cognitive therapy (MBCT) group
- Mirtazapine
- Non-directive/supportive/person-centred counselling
- Nortriptyline
- Paroxetine
- Peer support group
- Peer support group + any AD
- Problem solving individual
- Sertraline
- Short-term psychodynamic psychotherapy individual
- Supervised high intensity exercise group
- Supervised high intensity exercise group + sertraline
- Supervised high intensity exercise individual
- Supervised high intensity exercise individual + any AD
- Supervised high intensity exercise individual + sertraline
- Supervised low intensity exercise individual + any AD
- Third-wave cognitive therapy individual
- Third-wave cognitive therapy individual + any AD
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Trazodone
- Unsupervised high intensity individual
- Venlafaxine
- Yoga group + any AD

There is evidence suggesting Waitlist is the only intervention and class with a decreased odds in response compared to Pill placebo.

The classes for which there is evidence of an increased odds of response compared to Placebo are the following (supplement B5, Figure 5.12 in appendix 5):

- Acupuncture + AD
- Any AD
- Cognitive and cognitive behavioural therapies individual
- Cognitive and cognitive behavioural therapies individual + AD
- Exercise individual + AD
- Mindfulness or meditation group
- Mirtazapine
- Peer support group
- SNRIs

- SSRIs
- TCAs
- Trazodone
- Yoga group + AD

For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Mindfulness or meditation group is the highest ranked class at 1st (95% CrI 1st to 4th) (Table 134). The highest ranked intervention is Mindfulness-based cognitive therapy (MBCT) group with a posterior median rank of 1st (95% CrI 1st to 3rd) (Excel file in supplement B6: *"Depression NMA more severe RESPitt.xlsx"*, *"Ranks"* worksheet). The lowest ranked class and intervention is Waitlist, with a median class rank of 36th (95% CrI 33rd to 38th). The lowest ranked active class is Trazodone at 29th (95% CrI 24th to 33rd) (Table 134).

Table 134. Posterior mean and median rank and 95% credible intervals by class. Response in those randomised.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Mindfulness or meditation group	1.48	1 (1, 4)
Yoga group + AD	6.91	4 (1, 32)
Exercise individual + AD	8.25	7 (2, 25)
Cognitive and cognitive behavioural therapies individual + AD	8.39	7 (2, 21)
Peer support group	9.03	7 (2, 29)
Peer support group + AD	9.64	7 (1, 35)
Exercise group + AD	10.21	8 (2, 33)
Cognitive and cognitive behavioural therapies group + AD	10.36	7 (2, 36)
Behavioural therapies individual + AD	12.55	6 (1, 38)
Cognitive and cognitive behavioural therapies individual	13.92	14 (6, 24)
Light therapy + AD	14.44	12 (3, 36)
Behavioural therapies individual	14.87	13 (4, 35)
Self-help	15.07	14 (4, 34)
Short-term psychodynamic psychotherapies individual	16.16	15 (5, 32)
Acupuncture + AD	16.29	16 (10, 23)
Self-help with support	17.34	17 (6, 33)
Counselling individual + AD	17.97	15 (3, 38)
Interpersonal psychotherapy (IPT) individual	18.9	18 (5, 36)
Problem solving individual	19.43	18 (5, 36)
Light therapy	20.52	19 (2, 38)
Music therapy group	21.57	21 (5, 38)
Counselling individual	22.14	22 (6, 37)
Self-help + AD	22.42	22 (3, 38)
Mirtazapine	22.98	23 (18, 28)
Yoga group	23.32	24 (5, 38)
TCAs	23.45	23 (18, 29)
SNRIs	24.03	24 (19, 29)
Cognitive and cognitive behavioural therapies group	24.44	25 (7, 37)

Acupuncture	24.51	26 (6, 38)
Exercise individual	24.77	25 (10, 37)
Exercise group	25.93	27 (11, 37)
SSRIs	26.53	27 (22, 31)
Trazodone	28.71	29 (24, 33)
Sham acupuncture	30.33	34 (7, 38)
TAU	30.9	31 (23, 36)
Placebo	32.04	32 (28, 36)
Attention placebo	35.03	36 (27, 38)
Waitlist	36.17	36 (33, 38)

Outcome: SMD

This analysis was carried out on all patients randomized where possible, using WinBUGS code given in supplement B5, appendix 1. However, if trials only reported the number of completers then these were also included. After excluding trials with zero events in all arms and trials with the number events equal to the denominator in all arms, 146 trials reported CFB. Out of the remaining studies 172 reported baseline and follow-up scores (but not CFB) and 34 reported response (but not CFB or baseline and follow-up). This meant that 352 trials of 99 interventions and 50 classes were included in the analysis for this outcome (Table 135,

Figure 106, Figure 107). One study (Leinonen 2007), comparing Escitalopram versus Short-term psychodynamic psychotherapy individual + any AD, was excluded because it was causing convergence issues in the model.

The model was a reasonable fit to the data, with the exception of two very poorly fitting studies (Schweitzer 1991 and Sahranavard 2018). Schweitzer 1991 compared different regimens of venlafaxine, which may explain the poor fit for this study. Between-study heterogeneity and posterior mean residual deviance were slightly lower in the inconsistency model than in the random effects consistency model (supplement B5, Table 3.14 in appendix 3). The inconsistency model notably predicted the data in three studies much better than the consistency model, further adding evidence of inconsistency (

Figure 108).

As a prespecified sensitivity analysis, a bias-adjusted model that accounted for small-study effects was fitted. The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model (supplement B5, Table 3.14 in appendix 3), and the bias parameter was negative (-2.57; 95%CrI -3.65 to -1.51), indicating that smaller studies tended to favour active interventions versus inactive controls or counselling. Reported results are therefore based on the bias-adjusted random-effects NMA model. Results from the bias-adjusted model and from the base-case unadjusted model can be found in Excel files in supplement B6 ("*Depression NMA more severe SMD bias-adjusted.xlsx"* and *"Depression NMA more severe SMD base-case.xlsx"*, respectively).

Moderate between trials heterogeneity was found relative to the size of the intervention effect estimates ($\tau_{study} = 0.19\ (95\%\ CrI\ 0.15\ to\ 0.23)$). Relative effects are presented compared to Pill placebo (supplement B5, Figures 5.13 & 5.14 in appendix 5).

Table 135. Interventions, classes and number of patients (N) included in SMD analysis.

	Intervention	N	Class		N	Variance Sharing*
1	Pill placebo	12554	Placebo	1	12554	
2	Attention placebo	61	Attention placebo	2	61	
3	No treatment	504	No treatment	3	504	
4	Waitlist	526	Waitlist	4	526	
5	TAU	220	TAU	5	220	
6	Mirtazapine	1884	Mirtazapine	6	1884	
7	Trazodone	1072	Trazodone	7	1072	
8	Behavioural activation (BA) individual	368	Behavioural therapies individual	8	378	1
9	Behavioural therapy (Lewinsohn 1976) individual	10				
10	CBT individual (15 sessions or over)	626	Cognitive and cognitive behavioural therapies individual	9	1044	1
11	CBT individual (under 15 sessions)	369				
12	Dialectical behavioural therapy (DBT) individual	10				
13	Third-wave cognitive therapy individual	39				
14	CBT group (under 15 sessions)	165	Cognitive and cognitive behavioural therapies group	10	165	1
15	Problem solving individual	367	Problem solving individual	11	367	1
16	Problem solving group	47	Problem solving group	12	47	1
17	Non-directive/supportive/person-centred counselling	404	Counselling individual	13	404	1
18	Interpersonal psychotherapy (IPT) individual	146	Interpersonal psychotherapy (IPT) individual	14	146	1

19	Psychoeducational group programme	44	Psychoeducation group	15	44	1
20	Cognitive bibliotherapy	159	Self-help	16	344	2
21	Computerised-CBT (CCBT)	120				
22	Computerised attentional bias modification	26				
23	Mindfulness meditation CD	39				
24	Cognitive bibliotherapy with support	66	Self-help with support	17	267	3
25	Computerised-CBT (CCBT) with support	164				
26	Mindfulness meditation CD with support	19				
27	Relaxation training CD with support	18				
28	Dynamic interpersonal therapy (DIT) individual	73	Short-term psychodynamic psychotherapies individual	18	233	1
29	Short-term psychodynamic psychotherapy individual	160				
30	Music therapy group	12	Music therapy group	19	12	1
31	Mindfulness-based cognitive therapy (MBCT) group	15	Mindfulness or meditation group	20	15	1
32	Peer support group	39	Peer support group	21	39	1
33	Any psychotherapy	37	Any psychotherapy	22	37	1
34	CBT individual (15 sessions or over) + pill placebo	17	Cognitive and cognitive behavioural therapies individual + placebo	23	61	1
35	CBT individual (under 15 sessions) + pill placebo	44				
36	Interpersonal psychotherapy (IPT) individual + pill placebo	69	Interpersonal psychotherapy (IPT) individual + placebo	24	69	1
37	Non-directive/supportive/person-centred counselling + pill placebo	26	Counselling individual + placebo	25	26	1
38	Progressive muscle relaxation individual + pill placebo	11	Relaxation individual + placebo	26	11	1
39	Any SSRI	207	SSRIs	27	22018	4
40	Citalopram	2195				
41	Escitalopram	4930				
42	Fluoxetine	6031				
43	Paroxetine	5861				
44	Sertraline	2794				
45	Amitriptyline	2462	TCAs	28	4524	5
46	Any TCA	21				
47	Clomipramine	345				
48	Imipramine	1306				

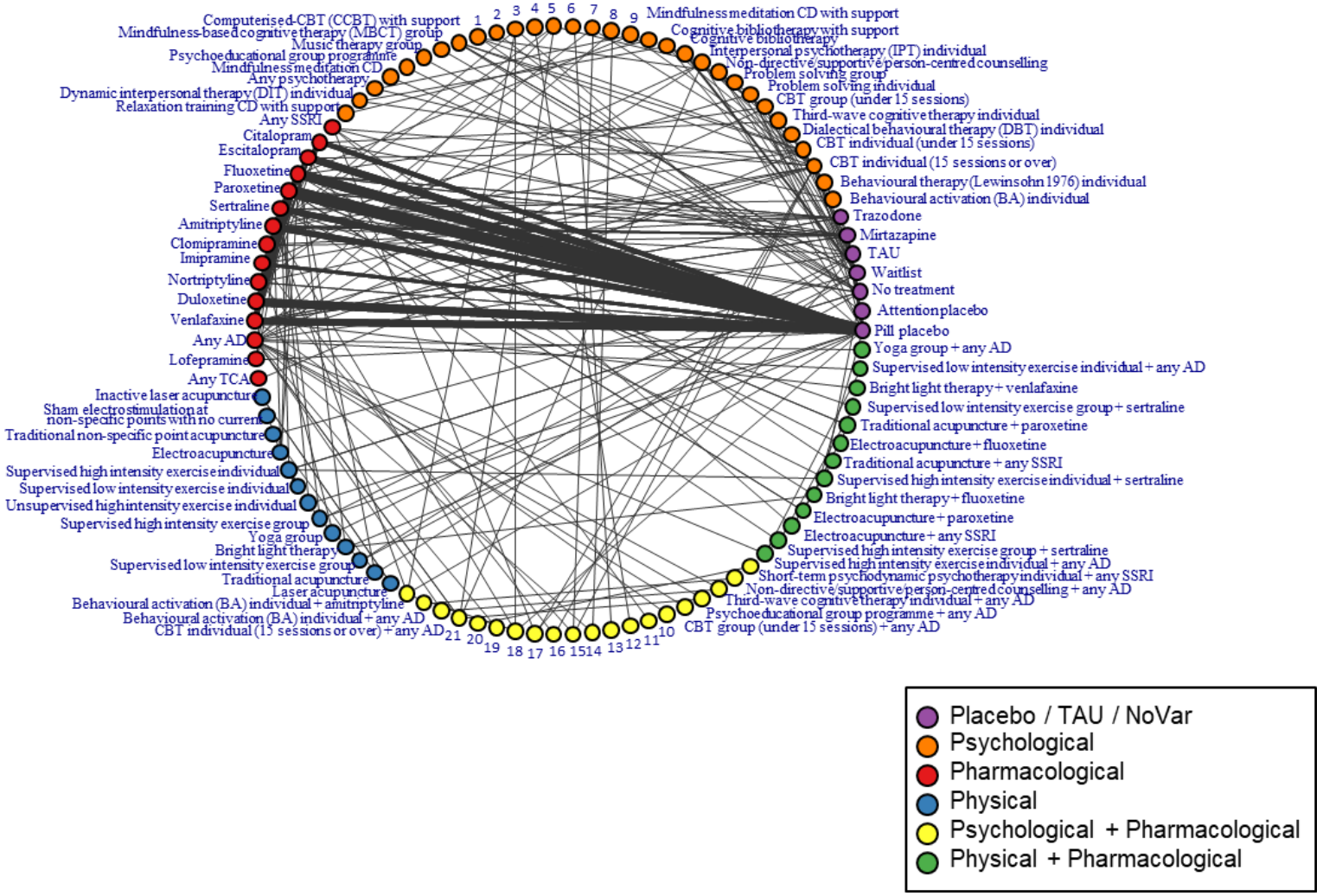
49	Lofepramine	145				
50	Nortriptyline	245				
51	Duloxetine	5269	SNRIs	29	9538	4
52	Venlafaxine	4269				
53	Any AD	452	Any AD	30	452	6
54	Inactive laser acupuncture	34	Sham acupuncture	31	108	1
55	Sham electrostimulation at non-specific points with no current	22				
56	Traditional non-specific point acupuncture	52				
57	Electroacupuncture	110	Acupuncture	32	264	1
58	Laser acupuncture	39				
59	Traditional acupuncture	115				
60	Supervised high intensity exercise individual	128	Exercise individual	33	298	7
61	Supervised low intensity exercise individual	117				
62	Unsupervised high intensity exercise individual	53				
63	Supervised high intensity exercise group	69	Exercise group	34	106	3
64	Supervised low intensity exercise group	37				
65	Yoga group	65	Yoga group	35	65	1
66	Bright light therapy	32	Light therapy	36	32	1
67	Behavioural activation (BA) individual + amitriptyline	12	Behavioural therapies individual + AD	37	22	8
68	Behavioural activation (BA) individual + any AD	10				
69	CBT individual (15 sessions or over) + any AD	10	Cognitive and cognitive behavioural therapies individual + AD	38	192	8
70	CBT individual (15 sessions or over) + any SSRI	43				
71	CBT individual (15 sessions or over) + imipramine	25				
72	CBT individual (15 sessions or over) + nortriptyline	18				
73	CBT individual (under 15 sessions) + escitalopram	48				
74	CBT individual (under 15 sessions) + sertraline	38				
75	Third-wave cognitive therapy individual + any AD	10				
76	CBT group (under 15 sessions) + any AD	63	Cognitive and cognitive behavioural therapies group + AD	39	63	8

77	Interpersonal counselling individual + venlafaxine	12	Interpersonal psychotherapy (IPT) individual + AD	40	99	8
78	Interpersonal psychotherapy (IPT) individual + any AD	87				
79	Non-directive/supportive/person-centred counselling + any AD	15	Counselling individual + AD	41	57	8
80	Non-directive/supportive/person-centred counselling + any SSRI	17				
81	Non-directive/supportive/person-centred counselling + fluoxetine	25				
82	Short-term psychodynamic psychotherapy individual + any AD	113	Short-term psychodynamic psychotherapies individual + AD	42	131	8
83	Short-term psychodynamic psychotherapy individual + any SSRI	18				
84	Psychoeducational group programme + any AD	27	Psychoeducation group + AD	43	27	8
85	Peer support group + any AD	42	Peer support group + AD	44	42	8
86	Progressive muscle relaxation individual + amitriptyline	10	Relaxation individual + AD	45	10	8
87	Supervised high intensity exercise individual + any AD	14	Exercise individual + AD	46	40	8
88	Supervised high intensity exercise individual + sertraline	15				
89	Supervised low intensity exercise individual + any AD	11				
90	Supervised high intensity exercise group + sertraline	42	Exercise group + AD	47	79	8
91	Supervised low intensity exercise group + sertraline	37				
92	Yoga group + any AD	15	Yoga group + AD	48	15	8
93	Electroacupuncture + any SSRI	160	Acupuncture + AD	49	584	9
94	Electroacupuncture + fluoxetine	46				
95	Electroacupuncture + paroxetine	71				
96	Traditional acupuncture + any SSRI	206				

97	Traditional acupuncture + paroxetine	101				
98	Bright light therapy + fluoxetine	29	Light therapy + AD	50	54	1
99	Bright light therapy + venlafaxine	25		50		

** Classes with the same number share a common class variance as described in methods, under 'Class models'*

Figure 106. Network diagram of every study included in analysis by intervention. SMD.



1 Computerised-CBT (C-CBT); 2 Computerised attentional bias modification; 3 Progressive muscle relaxation individual + pill placebo; 4 Non-directive/supportive/person-centred counselling + pill placebo; 5 Interpersonal psychotherapy (IPT) individual + pill placebo; 6 CBT individual (under 15 sessions) + pill placebo; 7 CBT individual (15 sessions or over) + pill placebo; 8 Peer support group; 9 Short-term psychodynamic psychotherapy individual; 10 Interpersonal counselling individual + venlafaxine; 11 CBT individual (under 15 sessions) + escitalopram; 12 Non-directive/supportive/person-centred counselling + fluoxetine; 13 CBT individual (under 15 sessions) + sertraline; 14 Peer support group + any AD; 15 CBT individual (15 sessions or over) + nortriptyline; 16 CBT individual (15 sessions or over) + imipramine; 17 CBT individual (15 sessions or over) + any SSRI; 18 Progressive muscle relaxation therapy + amitriptyline; 19 Short-term psychodynamic psychotherapy individual + any AD; 20 Non-directive/supportive/person-centred counselling + any SSRI; 21 Interpersonal psychotherapy (IPT) individual + any AD
Without the use of a class network the following interventions would be disconnected from the rest of the network and would have to be excluded from the analysis: Mindfulness meditation CD with support, CBT individual (under 15 sessions) + pill placebo, Non-directive/supportive/person-centred counselling + pill placebo, Inactive laser acupuncture, Behavioural activation (BA) individual + any AD, Non-directive/supportive/person-centred counselling + any SSRI, Relaxation training CD with support, CBT individual (under 15 sessions) + sertraline, Non-directive/supportive/person-centred counselling + fluoxetine, Laser acupuncture, Non-directive/supportive/person-centred counselling + any AD, and Short-term psychodynamic psychotherapy individual + any SSRI

Figure 107. Network diagram of every study included in analysis by class. SMD.

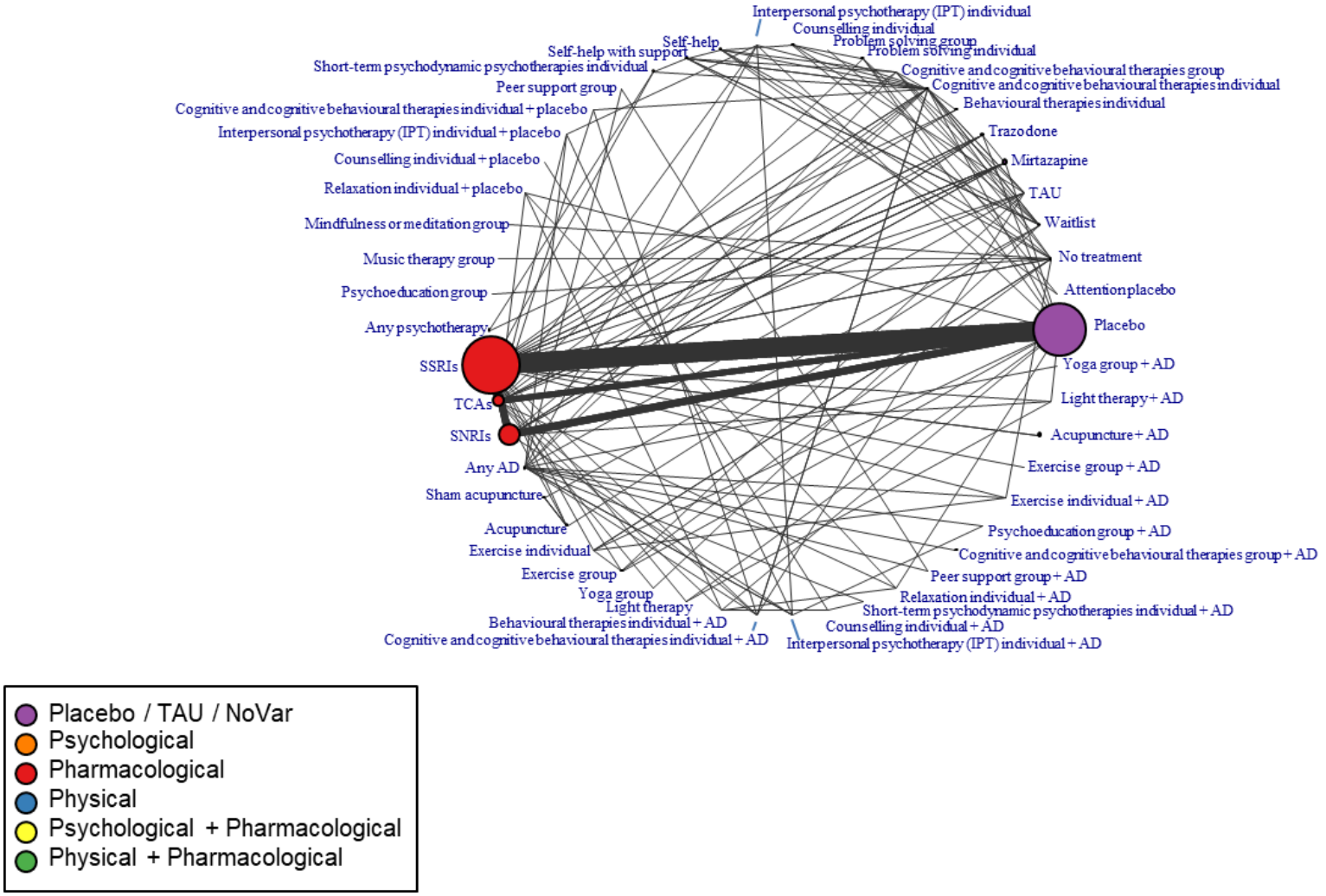
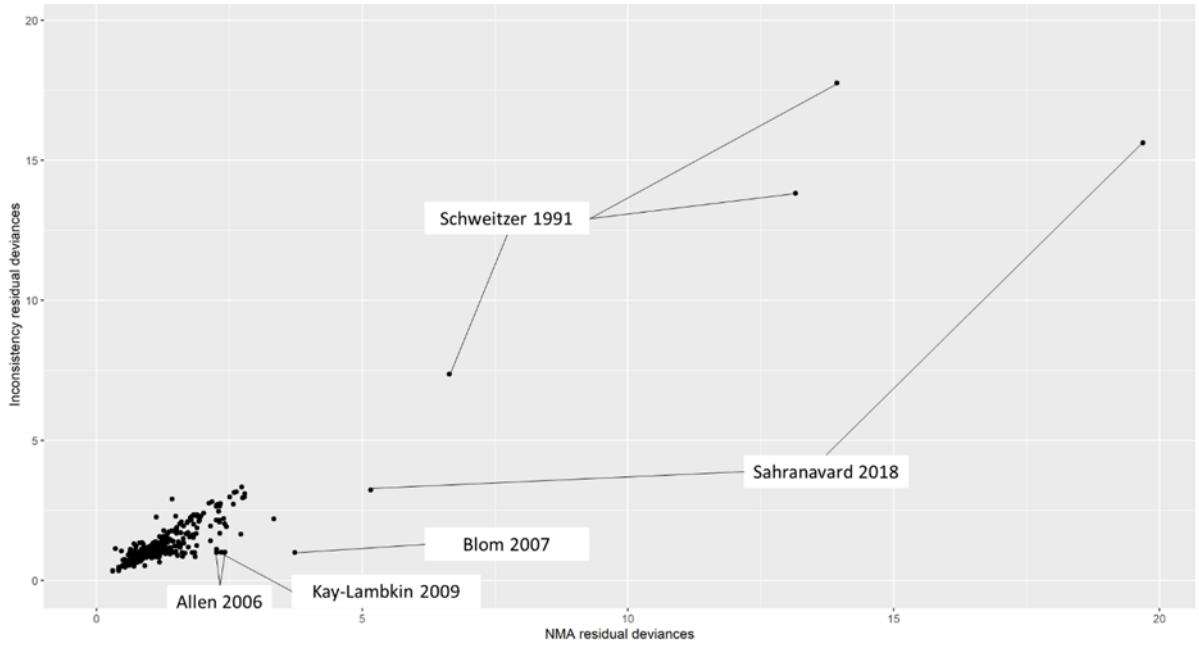


Figure 108. Deviance plot. SMD.



There is evidence that the following interventions have a lower standardized mean difference in depression compared to Pill placebo (supplement B5, Figure 5.13 in appendix 5):

- Amitriptyline
- Any AD
- Any SSRI
- Behavioural activation (BA) individual
- Behavioural therapy (Lewinsohn 1976) individual
- Bright light therapy
- Bright light therapy + fluoxetine
- Bright light therapy + venlafaxine
- CBT group (under 15 sessions) + any AD
- CBT individual (15 sessions or over)
- CBT individual (15 sessions or over) + any AD
- CBT individual (15 sessions or over) + any SSRI
- CBT individual (15 sessions or over) + imipramine
- CBT individual (under 15 sessions)
- CBT individual (under 15 sessions) + escitalopram
- CBT individual (under 15 sessions) + sertraline
- Citalopram
- Clomipramine
- Cognitive bibliotherapy
- Computerised-CBT (CCBT)
- Computerised-CBT (CCBT) with support
- Dialectical behavioural therapy (DBT) individual
- Duloxetine
- Dynamic interpersonal therapy (DIT) individual

- Electroacupuncture
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Electroacupuncture + paroxetine
- Escitalopram
- Fluoxetine
- Imipramine
- Interpersonal psychotherapy (IPT) individual
- Interpersonal psychotherapy (IPT) individual + any AD
- Lofepramine
- Mindfulness meditation CD
- Mindfulness-based cognitive therapy (MBCT) group
- Mirtazapine
- Non-directive/supportive/person-centred counselling
- Paroxetine
- Peer support group
- Peer support group + any AD
- Problem solving group
- Problem solving individual
- Psychoeducational group programme
- Sertraline
- Short-term psychodynamic psychotherapy individual
- Supervised high intensity exercise group + sertraline
- Supervised high intensity exercise individual + any AD
- Supervised low intensity exercise group + sertraline
- Third-wave cognitive therapy individual
- Third-wave cognitive therapy individual + any AD
- Traditional acupuncture
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Venlafaxine
- Yoga group
- Yoga group + any AD

The only class/intervention for which there was some evidence of having a higher standardized mean difference than Pill placebo was Waitlist.

The following classes have a lower standardized mean difference compared to Pill placebo (supplement B5, Figure 5.14 in appendix 5):

- Acupuncture + AD
- Any AD
- Behavioural therapies individual
- Cognitive and cognitive behavioural therapies individual
- Cognitive and cognitive behavioural therapies individual + AD
- Exercise group + AD

- Light therapy + AD
- Mindfulness or meditation group
- Mirtazapine
- Peer support group
- Problem solving group
- Problem solving individual
- Psychoeducation group
- SNRIs
- SSRIs
- TAU
- TCAs
- Yoga group
- Yoga group + AD

For many classes, effects were more uncertain than at the intervention-level due to high or poorly estimated variability of interventions within a class, particularly for psychological and physical therapies.

Mindfulness or meditation group is the highest ranked class at 1st (95% CrI 1st to 4th) (Table 136). The highest ranked intervention, Mindfulness-based cognitive therapy (MBCT) group, belongs to this class with a posterior median rank of 1st (95% CrI 1st to 3rd) (Excel file in supplement B6: *"Depression NMA more severe SMD bias-adjusted.xlsx"*, *"Ranks"* worksheet). The lowest ranked class and intervention is Waitlist, with a posterior median class rank of 39th (95% CrI 31st to 43rd). The lowest ranked active class and intervention is Trazodone, with a posterior median class rank of 34th (95% CrI 27th to 40th).

Table 136. Posterior mean and median rank and 95% credible intervals by class. SMD.

Class	Posterior mean rank	Posterior median rank (95% CrI)
Mindfulness or meditation group	1.41	1 (1, 4)
Problem solving group	3.76	3 (1, 12)
Yoga group + AD	7.82	4 (1, 38)
Peer support group	9.83	8 (3, 30)
Peer support group + AD	10.42	7 (2, 39)
Exercise group + AD	10.63	8 (2, 37)
Cognitive and cognitive behavioural therapies individual + AD	11.09	10 (4, 24)
Cognitive and cognitive behavioural therapies group + AD	12.86	9 (2, 40)
Psychoeducation group	14.18	12 (3, 36)
Yoga group	14.26	12 (3, 39)
Self-help	14.99	13 (3, 41)
Behavioural therapies individual	15.97	15 (5, 33)
Exercise individual + AD	15.98	13 (3, 40)
Light therapy + AD	16.07	15 (5, 34)
Problem solving individual	16.22	15 (5, 36)
Acupuncture + AD	16.88	17 (9, 26)
Cognitive and cognitive behavioural therapies individual	17.28	17 (8, 27)
Counselling individual	19.96	19 (7, 39)

Light therapy	20.89	20 (6, 40)
Self-help with support	21.32	20 (6, 41)
Interpersonal psychotherapy (IPT) individual + AD	21.32	20 (4, 42)
Short-term psychodynamic psychotherapies individual	22.08	22 (8, 38)
Interpersonal psychotherapy (IPT) individual	25.01	24 (8, 41)
Acupuncture	26.35	26 (12, 39)
Short-term psychodynamic psychotherapies individual + AD	26.51	29 (3, 43)
Psychoeducation group + AD	26.59	28 (4, 43)
Mirtazapine	27.04	27 (20, 34)
Behavioural therapies individual + AD	28.06	35 (2, 43)
SNRIs	28.07	28 (22, 34)
Sham acupuncture	28.47	29 (12, 41)
TAU	28.96	29 (19, 38)
Relaxation individual + AD	29.23	38 (2, 43)
TCAs	29.34	29 (21, 37)
Music therapy group	29.54	34 (5, 43)
Cognitive and cognitive behavioural therapies group	29.59	31 (11, 42)
Exercise group	30.6	32 (10, 42)
SSRIs	31.21	31 (25, 37)
Exercise individual	31.75	34 (9, 43)
Counselling individual + AD	32.21	40 (4, 43)
Attention placebo	32.27	34 (15, 42)
Trazodone	34.14	34 (27, 40)
Placebo	37	37 (32, 41)
Waitlist	38.83	39 (31, 43)

Assumptions and limitations

- We assumed that our methods for converting baseline and final and response data to CFB would give reliable estimates of CFB. These equations are based on a mathematical relationship with the assumption of normality of the underlying continuous data. As mentioned in the methods section we checked these assumptions by looking at the observed data for studies reporting all outcomes and found good agreement, however this may not apply to the other studies.
- Similarly we assumed that the method we used to convert SMD to response gave reliable estimates of response. This method is well known and recommended by the Cochrane Collaboration, although it is an approximation and may perform poorly at $-5 \geq \ln(OR) \geq 5$ (Chinn 2000).
- For the SMD analysis we needed to make an assumption about the relationship between the standard deviation at baseline and standard deviation at follow-up. Based on an analysis of studies which reported both, we assumed that these were equal.
- We assumed the existence of class effects and modelled the data in this way. For classes with only one or two interventions we needed to make some assumptions about the variance of those classes. However, this did allow for fitting a more flexible model than could otherwise be achieved by fitting fewer class variances. The assumptions we made are highlighted in the report and informed by clinical opinion from members of the guideline committee.
- We assumed additivity of TAU efficacy when given in combination with other treatments. This meant that if TAU was given with other treatments in all arms in a study, we assumed

that the relative effects of the different treatments in each arm would be the same as in a similar study in which TAU was not given in any arms. We assessed the impact of this by fitting a model that assumed a multiplicative effect and found no difference in model fit (see below under '*Post-hoc sensitivity analyses*').

- For estimating the indirect evidence contributions from inconsistency models we assumed that the posterior distributions of relative effects were normally distributed. Whilst they were generally approximately normal, deviations from normality in some cases may have affected our findings regarding which comparisons had significant discrepancies between direct and indirect evidence.

Sensitivity analyses: prespecified

A key assumption in NMA is that of transitivity – i.e. that the balance of effect modifiers (factors that influence the treatment effect) is similar across all trials in the network. In order to explore the validity of this assumption, pre-specified sensitivity analyses were conducted. We also further explored this key assumption using several additional sensitivity analyses that were conducted post-hoc (see 'Sensitivity analyses: post-hoc' below).

In this section we present forest plots comparing relative effects versus a common reference treatment for several prespecified sensitivity analyses.

Table 137 shows the number of RCTs included in the NMAs on the SMD outcome that were rated as low, unclear or high risk of bias for different domains of the RoB tool, for both less and more severe depression.

Table 137. Number of RCTs according to risk of bias ratings for each domain in the NMAs on the SMD outcome for less and more severe depression

Domain	Less severe depression			More severe depression		
	Risk rating			Risk rating		
	Low	Unclear	High	Low	Unclear	High
Allocation Method	52	51	24	77	235	39
Allocation Concealment	48	76	3	70	281	0
Blinding (Participants)	6	14	107	232	12	107
Blinding (Care Adminstrator)	8	9	110	229	11	111
Performance	6	12	109	229	15	107
Detection	13	113	1	61	270	20
Attrition	79	30	18	239	93	19
Selective Reporting	22	78	27	62	123	166

For many domains, there were insufficient studies to analyse a low risk of bias subgroup. We conducted post-hoc sensitivity analyses in the subgroups of studies rated as low risk for attrition (see 'Sensitivity analyses: post-hoc').

Boxplots of risk of bias domains by the number of participants randomised per study arm are shown for less severe depression (Figure 109) and more severe depression (Figure 110). These show that smaller studies are at higher risk of bias across almost all domains in both less and more severe depression.

Figure 109. Boxplots showing the number of participants randomised per study arm by risk of bias rating for each risk of bias domain in less severe depression

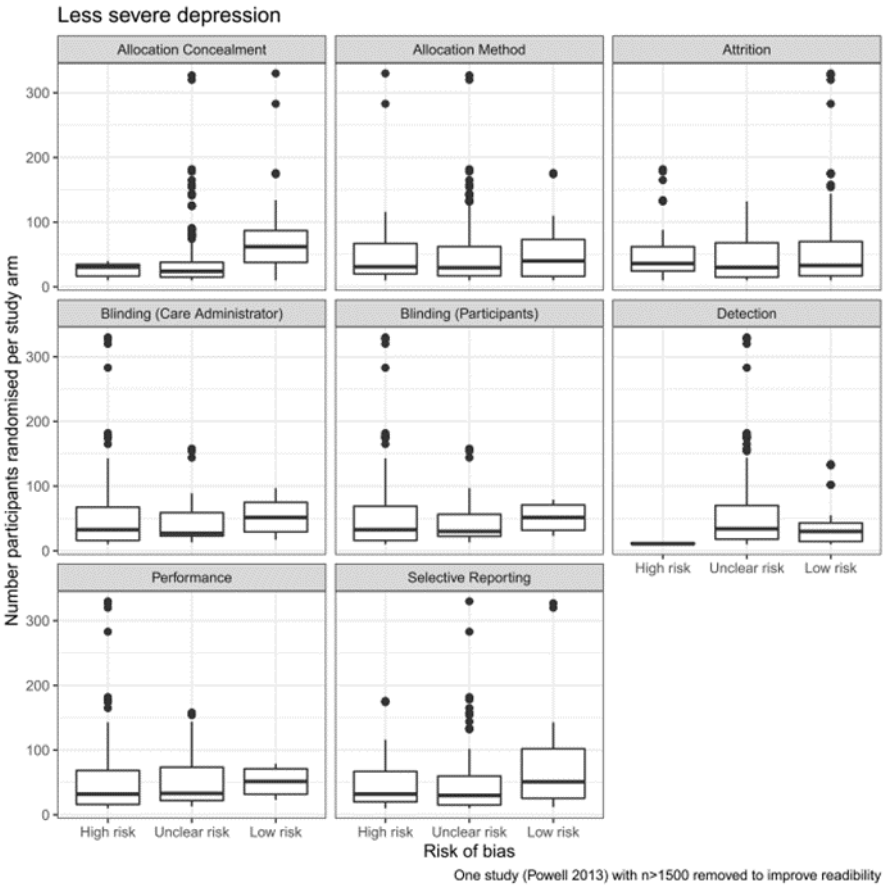
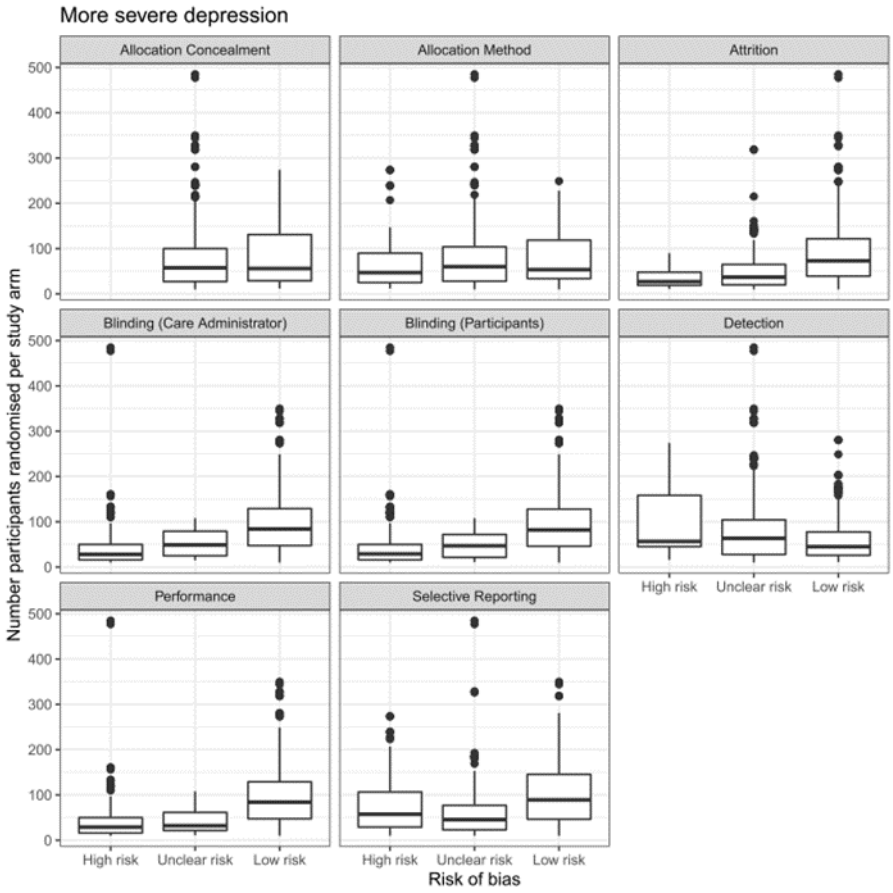


Figure 110. Boxplots showing the number of participants randomised per study arm by risk of bias rating for each risk of bias domain in more severe depression

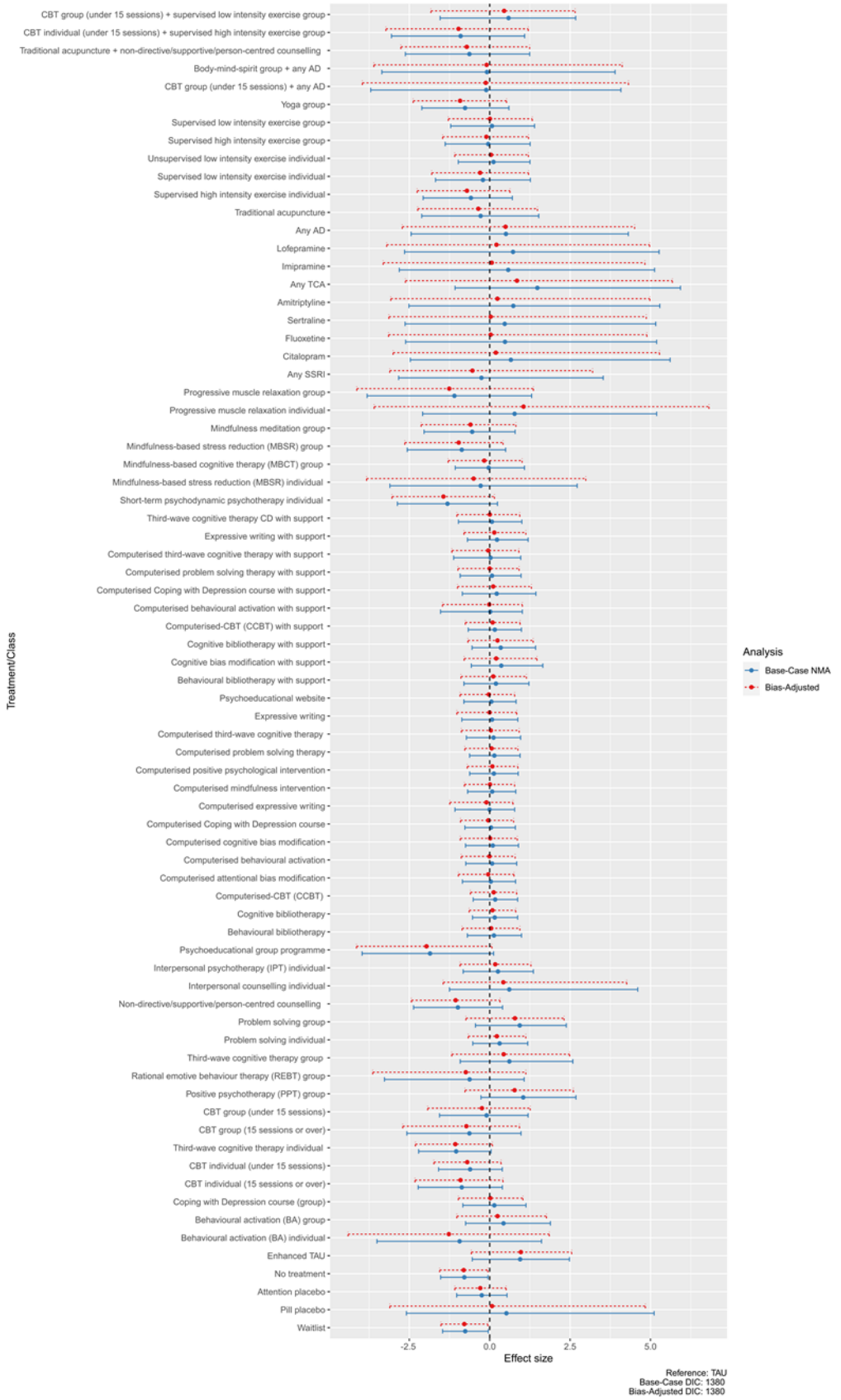


Less severe depression – Discontinuation (for any reason)

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to TAU for most interventions, and minimal reductions in efficacy for pharmacological interventions (Lofepramine, Imipramine, Any TCA, Amitriptyline, Sertraline, Fluoxetine, Citalopram, Pill placebo) and classes (TCAs, SSRIs, Placebo) (Figure 111 and Figure 112). 95%CrIs for relative effects were slightly wider in the bias-adjusted model, and this effect was typically greater for treatments / classes for which there was high uncertainty.

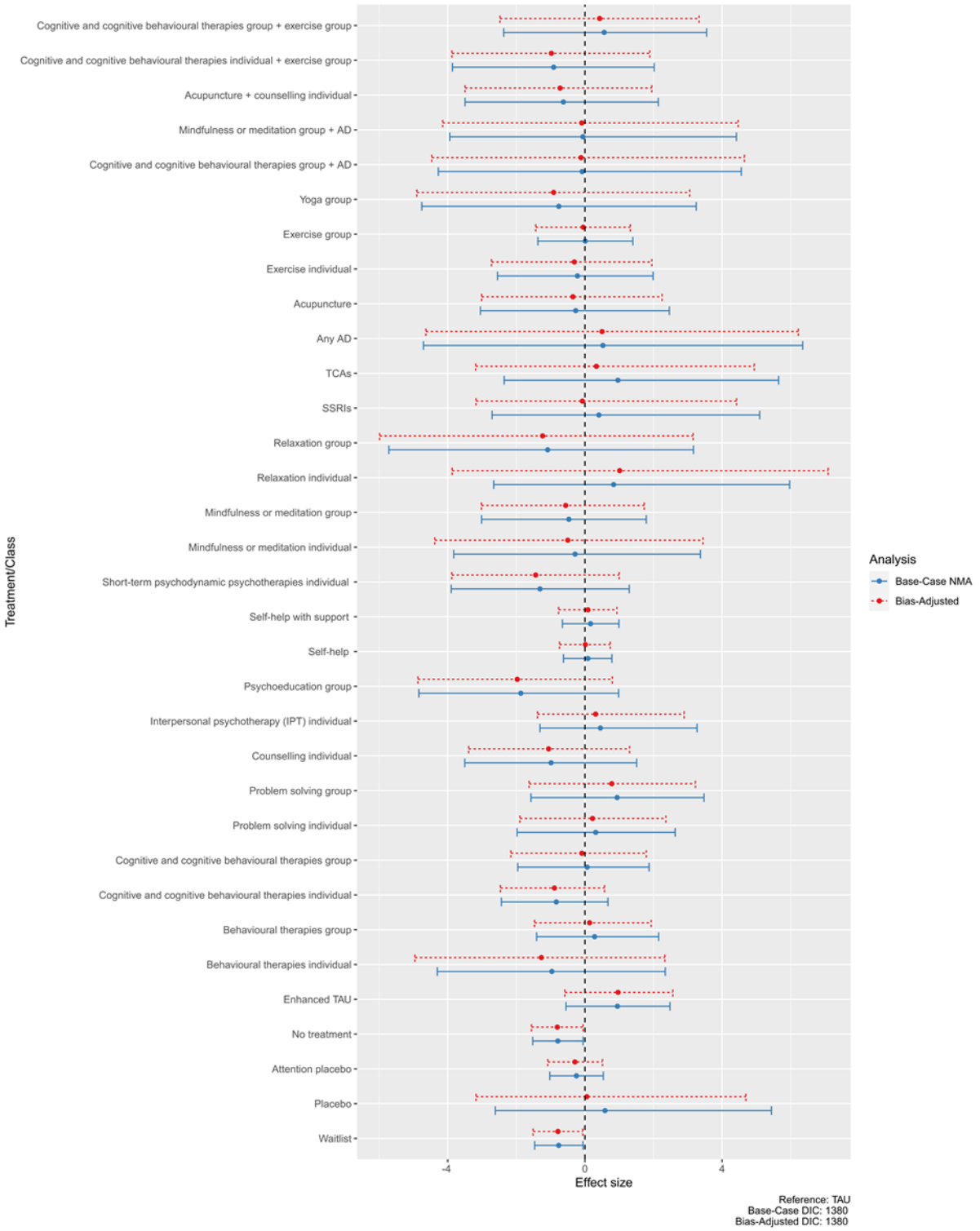
Although the between study heterogeneity was slightly lower in the bias-adjusted model (supplement B5, Table 3.1 in appendix 3; Figure 72), the DIC remained the same as in the base-case consistency model. For this reason, results are reported for the base-case model.

Figure 111: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in less severe depression for each intervention versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 112: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in less severe depression for each class versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

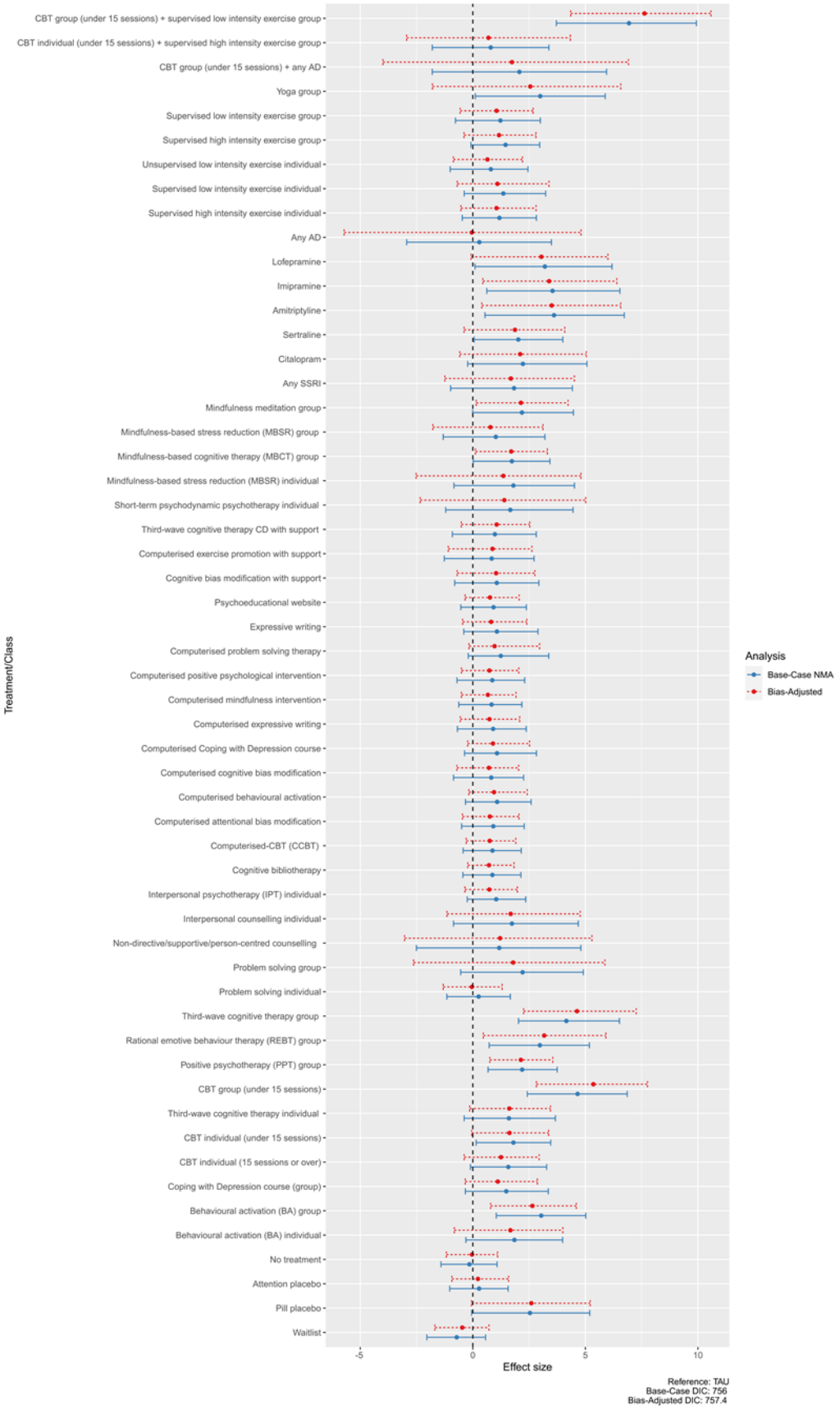
Less severe depression – Response in completers

Results were similar between base-case and bias-adjusted NMA models, with only very minimal changes in relative effects compared to TAU for most interventions that was generally towards zero (i.e. a smaller effect) in the bias-adjusted model compared to the base-case. There was an increase in efficacy versus TAU in the bias-adjusted model

compared to the base-case model in CBT group (under 15 sessions) and CBT group (under 15 sessions) + supervised low intensity exercise group, though this change was less noticeable at the class level (Figure 113 and Figure 114).

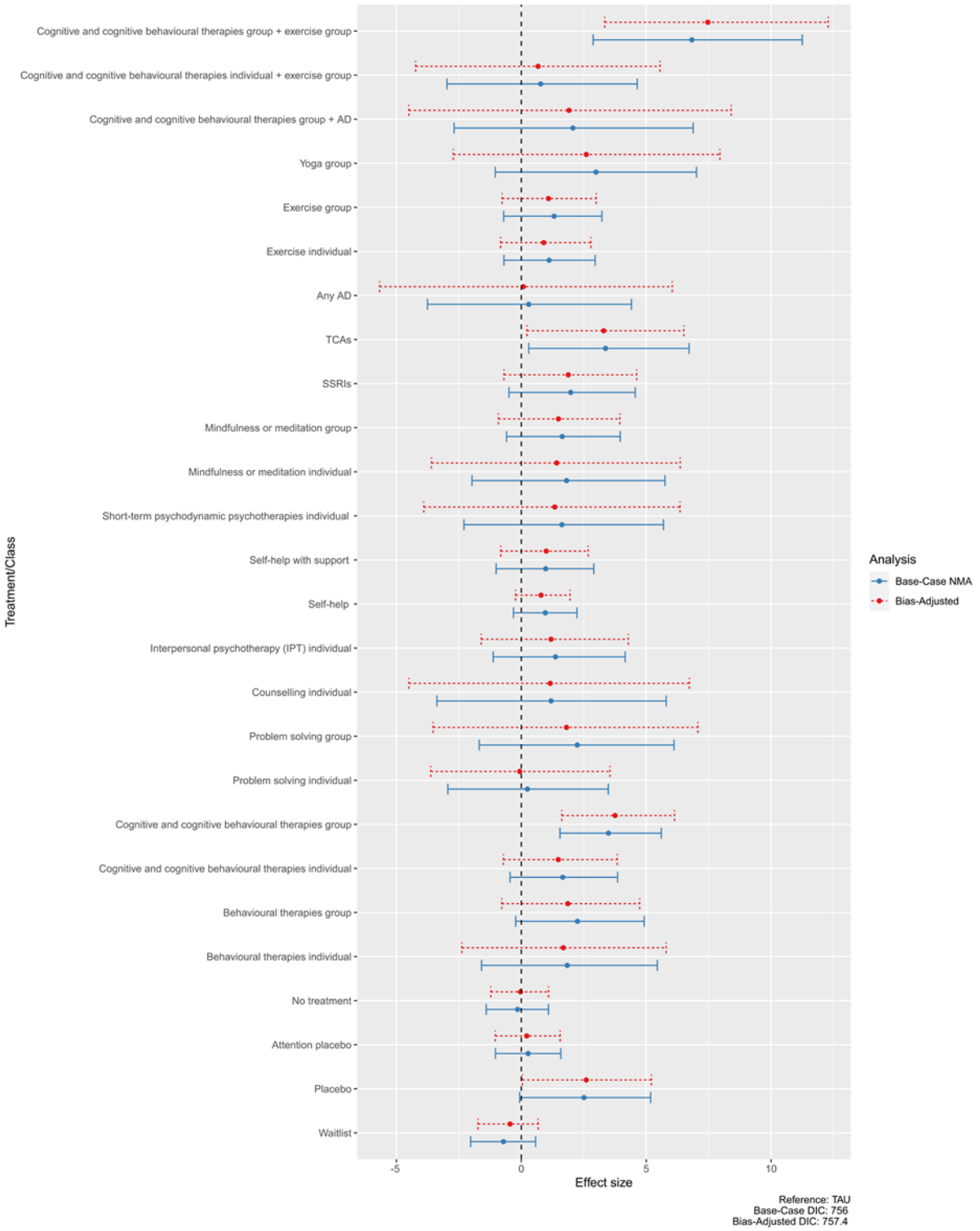
Although the DIC between the models, the between study heterogeneity was substantially reduced (supplement B5, Table 3.5 in appendix 3) in the bias-adjusted random-effects NMA model, and the prediction of data points improved. Reported results are therefore based on the bias-adjusted random-effects NMA model.

Figure 113: Log-odds ratios and 95% credible intervals for response in completers in less severe depression for each intervention versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 114: Log-odds ratios and 95% credible intervals for response in completers in less severe depression for each class versus TAU.

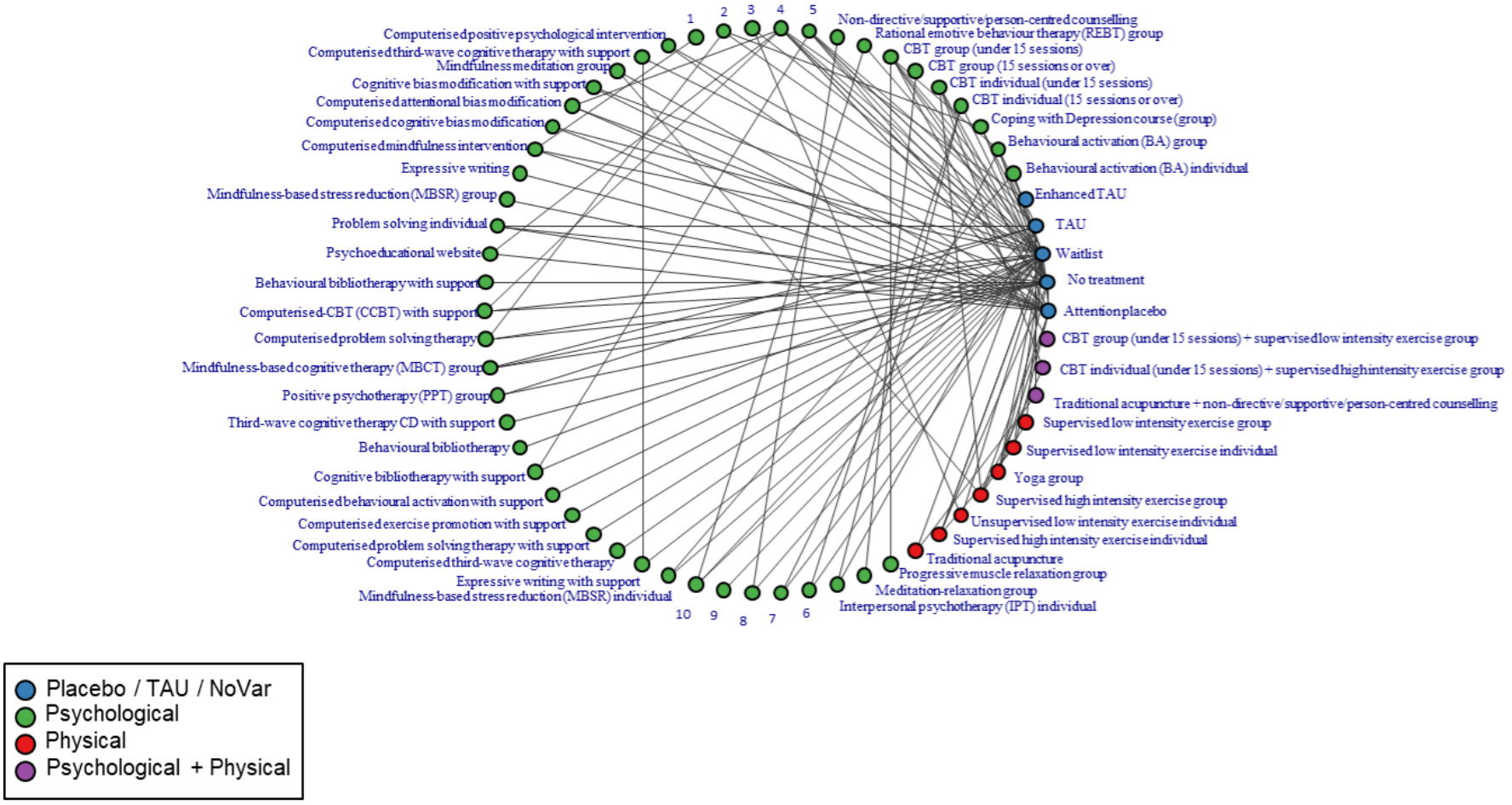


Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Less severe depression – SMD

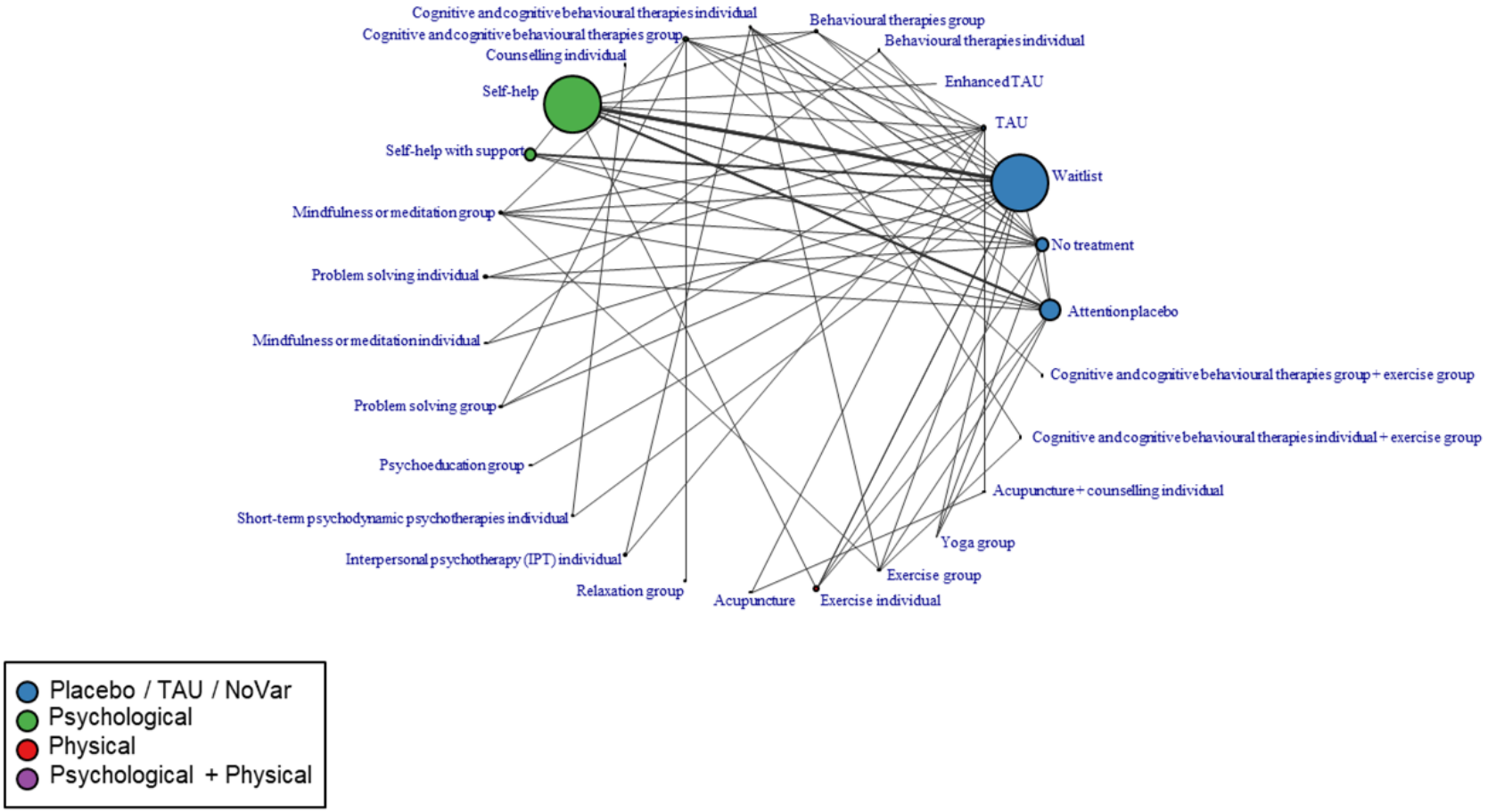
The network diagrams for the analysis of studies that included non-pharmacological interventions only are shown in Figure 115 and Figure 116.

Figure 115. Network diagram of every study included in analysis by intervention. SMD for non-pharmacological interventions.



1 Computerised expressive writing; 2 Computerised Coping with Depression Course; 3 Computerised behavioural activation; 4 Computerised-CBT (CCBT); 5 Cognitive bibliotherapy; 6 Third-wave cognitive therapy individual; 7 Third-wave cognitive therapy group; 8 Short-term psychodynamic psychotherapy individual; 9 Psychoeducational group programme; 10 Problem solving group

Figure 116. Network diagram of every study included in analysis by class. SMD for non-pharmacological interventions.



Compared to results from the base-case NMA model, estimates for most interventions versus TAU from the non-pharmacological interventions only NMA were very similar. However, the efficacy versus TAU was lower in the non-pharmacological interventions-only NMA for Supervised high intensity exercise group, Supervised low intensity exercise individual and Supervised high intensity exercise individual (Figure 117). At the class level, although posterior medians were similar in the two models, 95%CrIs for most classes were slightly wider in non-pharmacological interventions-only NMA, reflecting the reduction in information in the network with which to estimate class effects and variances (Figure 118). For Exercise group and Exercise individual 95%CrIs were substantially narrower than in the base-case NMA.

There were some differences between results from the bias-adjusted NMA and base-case NMA models, though these typically varied in direction. This led to less clear evidence of efficacy versus TAU for the following interventions in the bias-adjusted model compared to the base-case model (Figure 117):

- Behavioural activation (BA) individual
- CBT individual (under 15 sessions)
- Rational emotive behavioural therapy (REBT) group
- Interpersonal psychotherapy (IPT) individual
- Meditation-relaxation group
- Supervised high intensity exercise group
- Yoga group

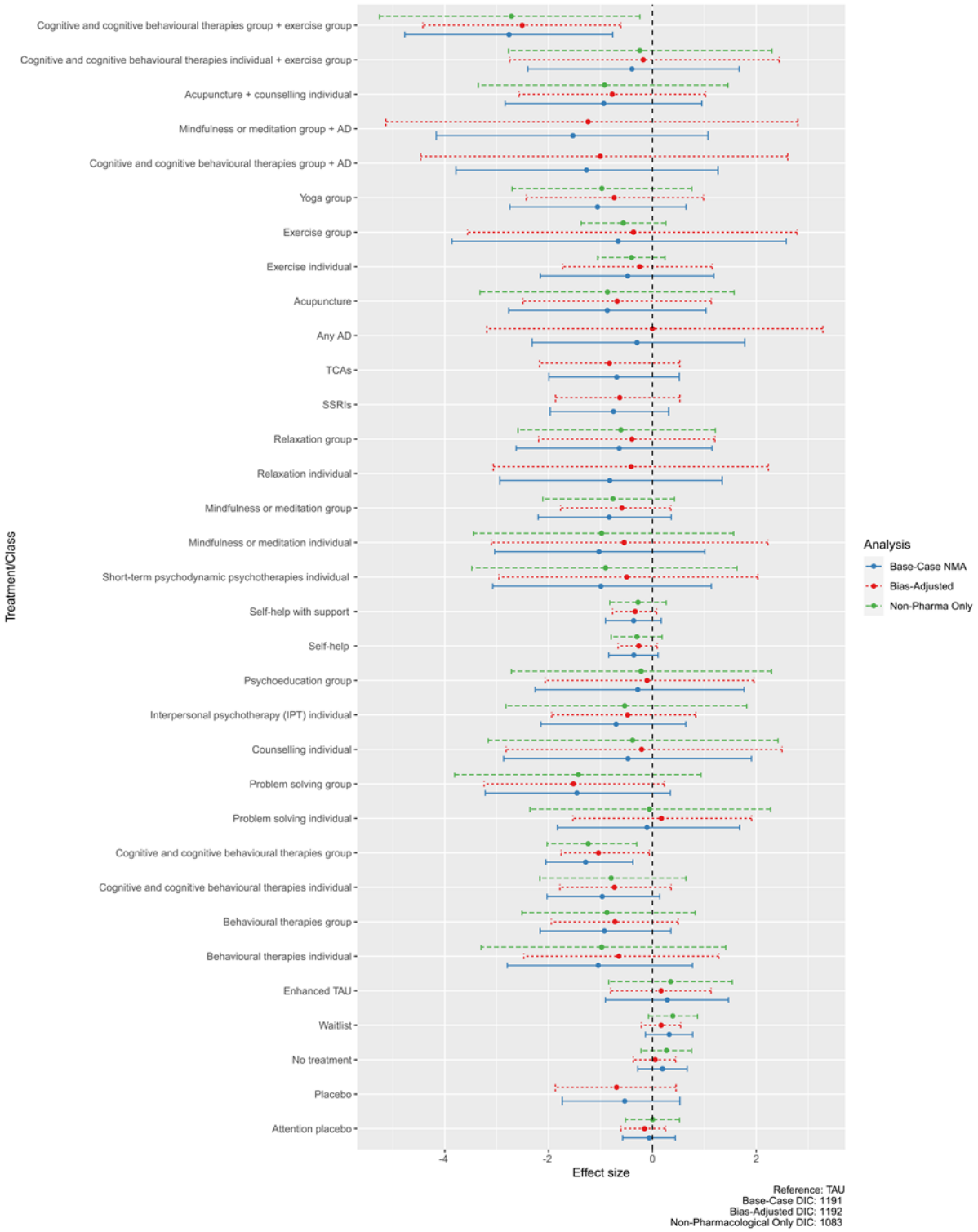
Differences in estimates between the bias-adjusted and base-case models were smaller for classes and are unlikely to have changed any conclusions regarding any class's efficacy versus TAU (Figure 118).

Between study heterogeneity and posterior mean residual deviance were lower in the bias-adjusted model than in the base-case model (supplement B5, Table 3.7 in appendix 3). Reported results were therefore based on the bias-adjusted random-effects NMA model, assuming consistency.

Figure 117: Standardised Mean Differences and 95% credible intervals for symptom severity in less severe depression for each intervention versus TAU.

Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, bias-adjusted results by a short-dashed red line, and non-pharmacological interventions only NMA results by a long-dashed green line.

Figure 118: Standardised Mean Differences and 95% credible intervals for symptom severity in less severe depression for each class versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, bias-adjusted results by a short-dashed red line, and non-pharmacological interventions only NMA results by a long-dashed green line.

More severe depression – Discontinuation (for any reason)

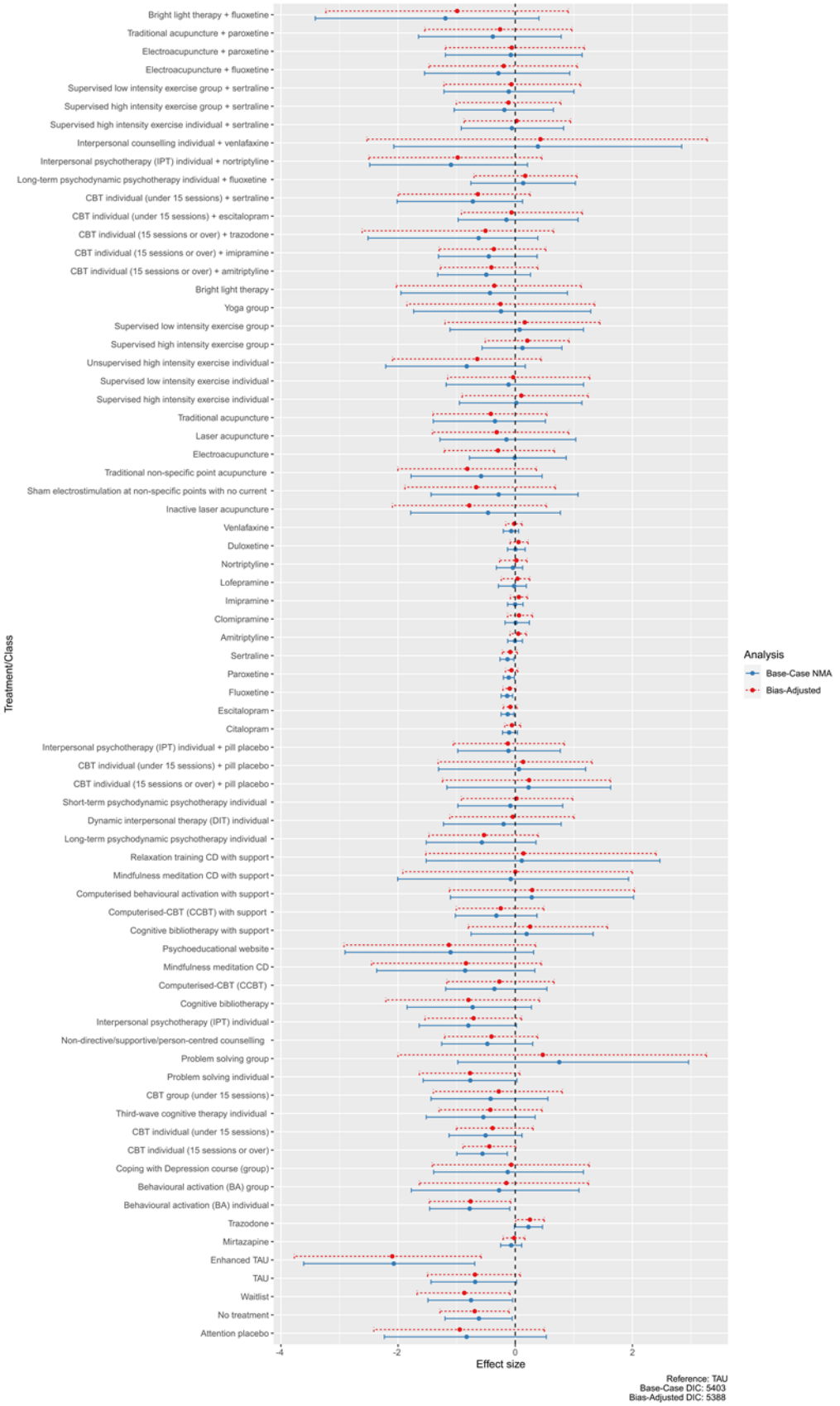
There were some differences between results from the bias-adjusted NMA and base-case NMA models, though these typically varied in direction. 95%CrIs were slightly wider for all estimates in the bias-adjusted model. In particular, estimates differed substantially for sham

and active acupuncture (Inactive laser acupuncture, Sham electrostimulation at non-specific points with no current, Traditional non-specific point acupuncture, Electroacupuncture, Laser acupuncture) versus TAU between the base-case and bias-adjusted models, due to small studies informing these interventions (Figure 119).

Differences between the models were smaller for classes, though 95%CrIs were also slightly wider for all estimates in the bias-adjusted model (Figure 120).

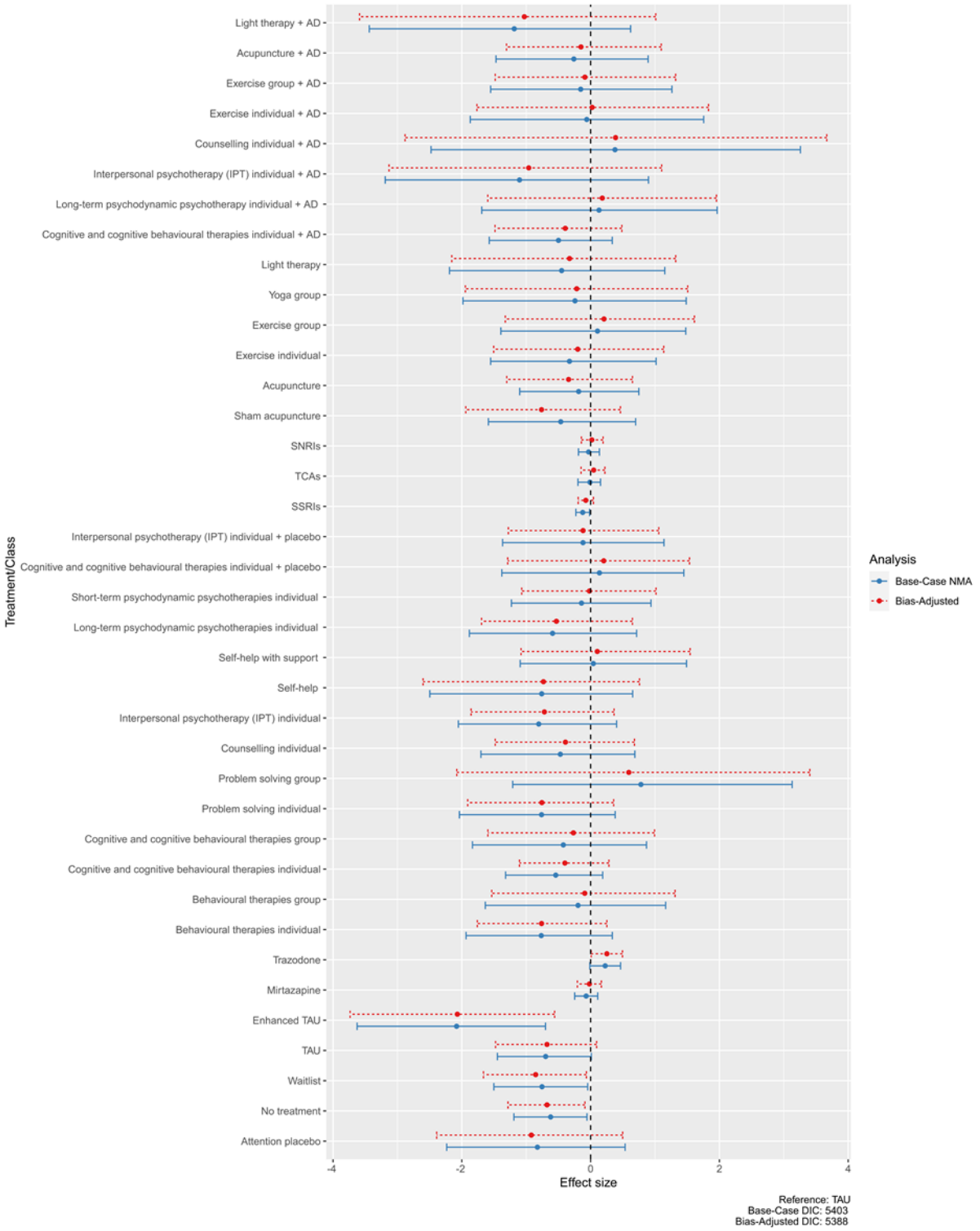
The between study heterogeneity was slightly reduced and the DIC was lower than in the base-case consistency model (supplement B5, Table 3.8 in appendix 3). For this reason, results are reported for the base-case model.

Figure 119: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in more severe depression for each intervention versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 120: Log-odds ratios and 95% credible intervals for discontinuation due to any reason in more severe depression for each class versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

More severe depression – Response in completers

There were some clear differences between results from the bias-adjusted NMA and base-case NMA models. Intervention estimates from the bias-adjusted model indicated lower response versus TAU than in the base-case model, leading to less clear evidence of efficacy

versus TAU for the following interventions in the bias-adjusted compared to the base-case model (Figure 121):

- Behavioural activation (BA) individual
- Behavioural therapy (Lewinsohn 1976) individual
- CBT individual (under 15 sessions)
- Third-wave cognitive therapy individual
- Dynamic interpersonal therapy (DIT) individual
- CBT individual (15 sessions or over) + pill placebo
- Any AD
- Yoga group
- CBT group (under 15 sessions) + Any AD

There were also very large reductions in efficacy versus TAU for the following interventions:

- Progressive muscle relaxation individual + amitriptyline
- Behavioural activation (BA) + any AD
- Behavioural activation (BA) + amitriptyline
- Supervised low intensity exercise individual
- Supervised high intensity exercise individual

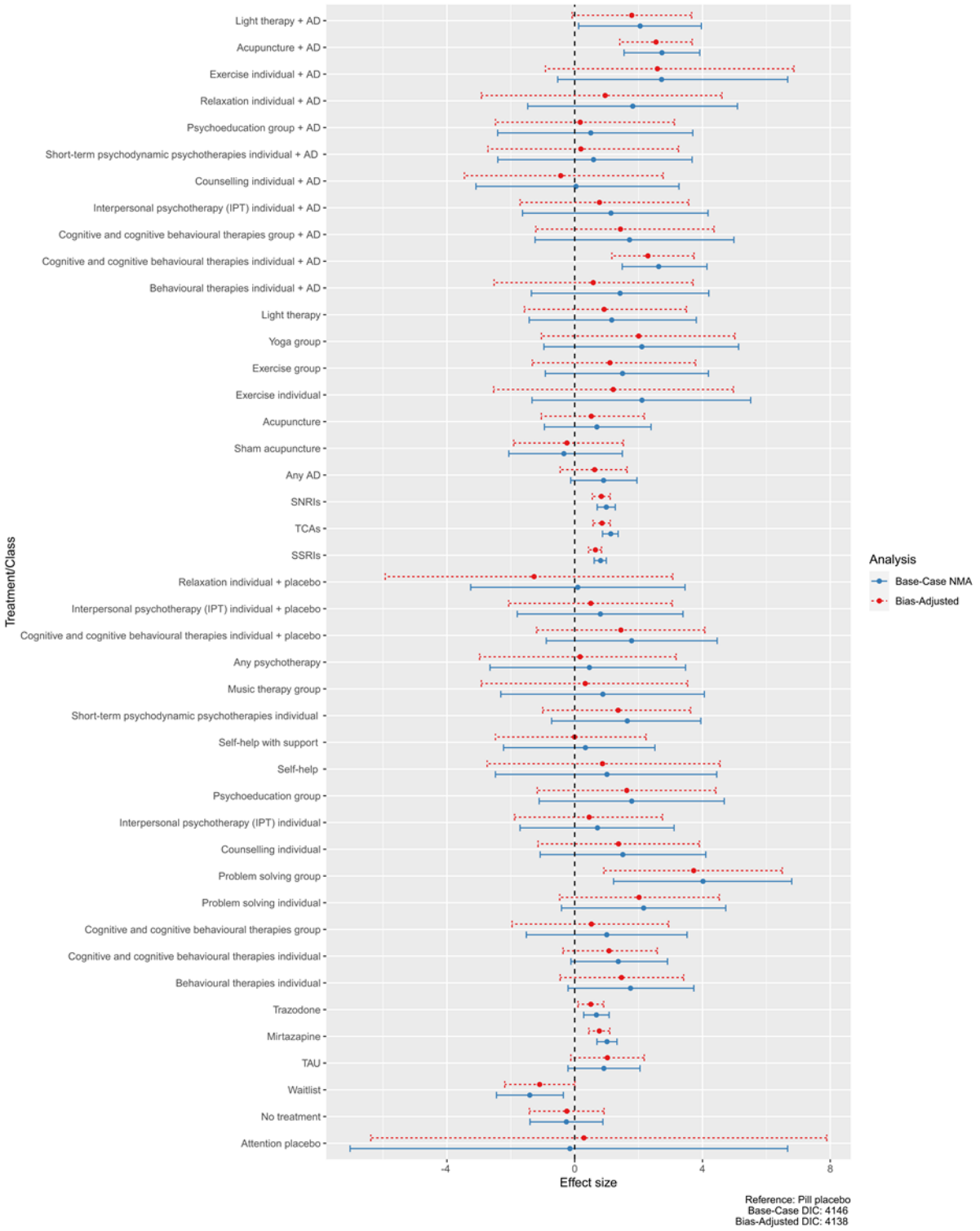
Differences between the models were smaller for classes, though 95%CrIs were also slightly wider for all estimates in the bias-adjusted model (Figure 122Figure 120).

The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model (supplement B5, Table 3.12 in appendix 3). Reported results are therefore based on the bias-adjusted random-effects NMA model.

Figure 121: Log-odds ratios and 95% credible intervals for response in completers in more severe depression for each intervention versus Pill placebo.

Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

Figure 122: Log-odds ratios and 95% credible intervals for response in completers in more severe depression for each class versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line and bias-adjusted results by a dashed red line.

More severe depression – SMD

The network diagrams for the analysis of studies that included non-pharmacological interventions only are shown in Figure 123 and Figure 124.

Figure 123. Network diagram of every study included in analysis by intervention. SMD for non-pharmacological interventions.

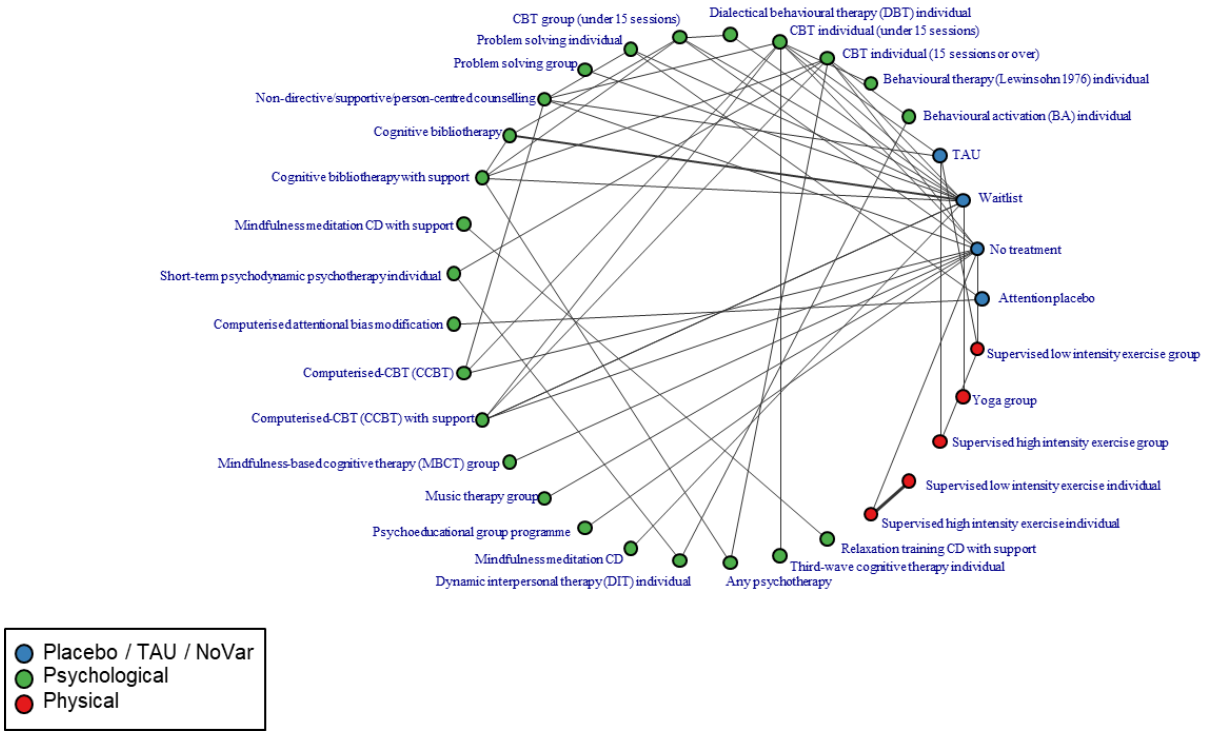
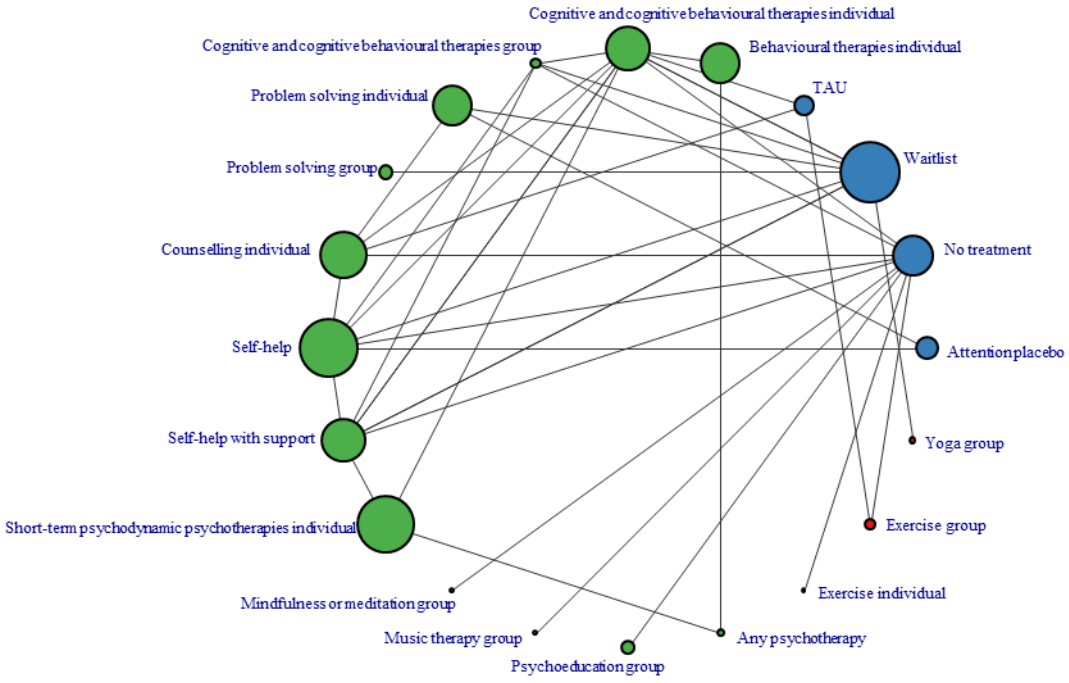


Figure 124. Network diagram of every study included in analysis by class. SMD for non-pharmacological interventions.



There were some significant differences in results between the base-case NMA model and the non-pharmacological interventions-only NMA. For all interventions and classes, 95%CrIs

were narrower in the base-case model. However, for the following interventions there were also substantial differences in the posterior medians of relative effects versus TAU, with a reduction in SMD versus TAU in the non-pharmacological interventions-only NMA compared to the base-case NMA (Figure 125):

- Attention placebo
- Behavioural activation (BA) individual
- CBT individual (15 sessions or over)
- Third-wave cognitive therapy
- CBT group (under 15 sessions)
- Computerised attentional bias modification
- Mindfulness medication CD
- Short-term psychodynamic psychotherapy individual
- Any psychotherapy
- Supervised high intensity exercise individual
- Supervised low intensity exercise individual

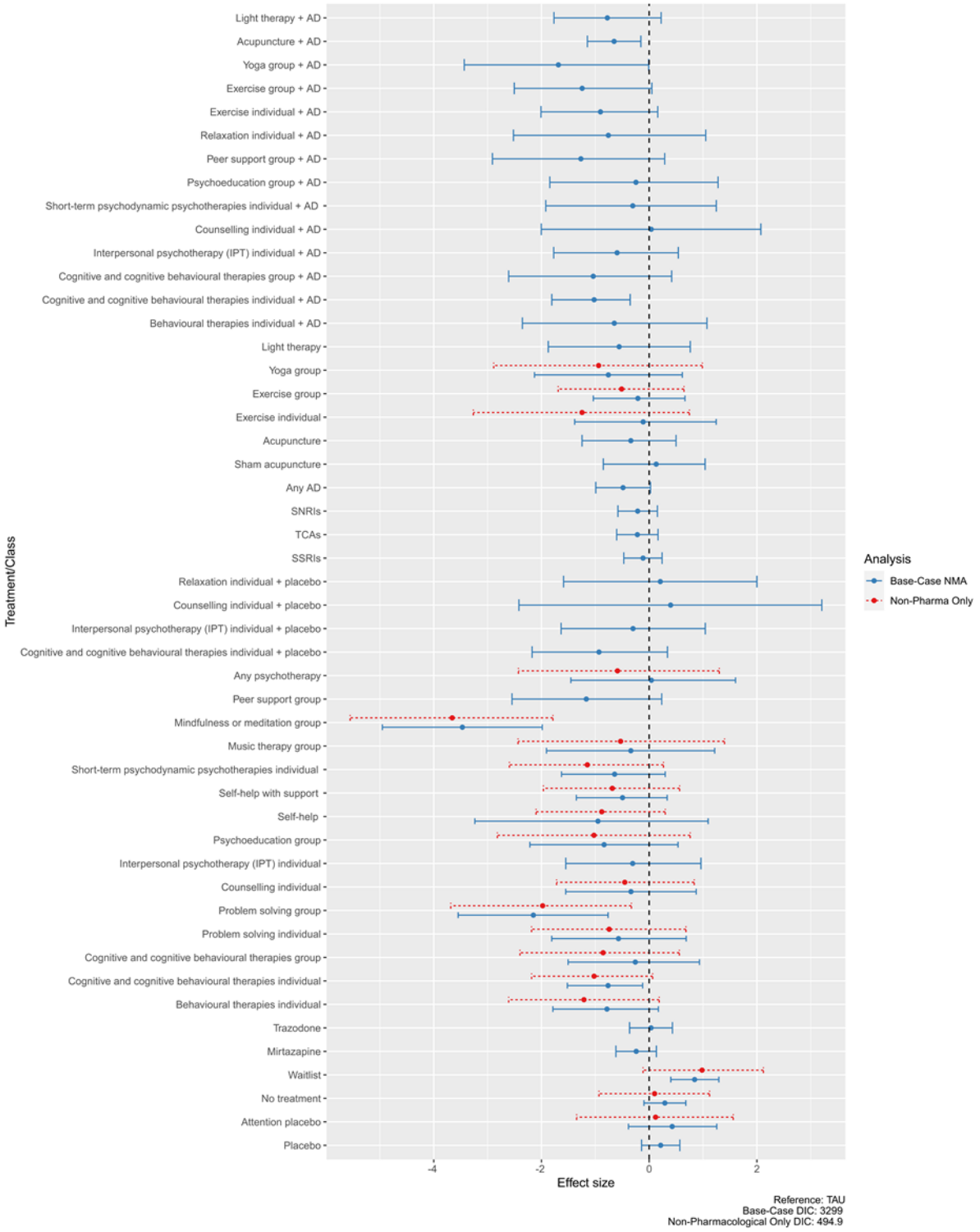
For the following classes there were substantial differences in relative effects versus TAU, with a reduction in SMD versus TAU in the non-pharmacological interventions-only NMA compared to the base-case NMA (Figure 126):

- Attention placebo
- Behavioural therapies individual
- Cognitive and cognitive behavioural therapies group
- Short-term psychodynamic psychotherapies individual
- Any psychotherapy
- Exercise individual

Figure 125: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each intervention versus TAU.

Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, non-pharmacological interventions-only results by a short-dashed red line.

Figure 126: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each class versus TAU.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, non-pharmacological interventions-only results by a short-dashed red line.

There were also some substantial differences between results from the bias-adjusted NMA and base-case NMA models, with relative effects from the bias-adjusted model typically indicating less efficacy versus TAU than those from the base-case model. This led to less clear evidence of efficacy versus TAU for the following interventions in the bias-adjusted model compared to the base-case model (Figure 127):

- Behavioural activation (BA) individual

- Behavioural therapy (Lewinsohn 1976) individual
- CBT individual (15 sessions or over)
- CBT individual (under 15 sessions)
- Dialectical behavioural therapy (DBT) individual
- Dynamic interpersonal therapy (DIT) individual
- CBT individual (15 sessions or over) + pill placebo
- CBT individual (15 sessions or over) + any SSRI
- CBT individual (15 sessions or over) + imipramine
- CBT individual (under 15 sessions) + sertraline
- Interpersonal psychotherapy (IPT) individual + any AD
- Supervised high intensity exercise individual + any AD
- Supervised low intensity exercise group + sertraline
- Electroacupuncture + any SSRI
- Electroacupuncture + fluoxetine
- Traditional acupuncture + any SSRI
- Traditional acupuncture + paroxetine
- Bright light therapy + fluoxetine

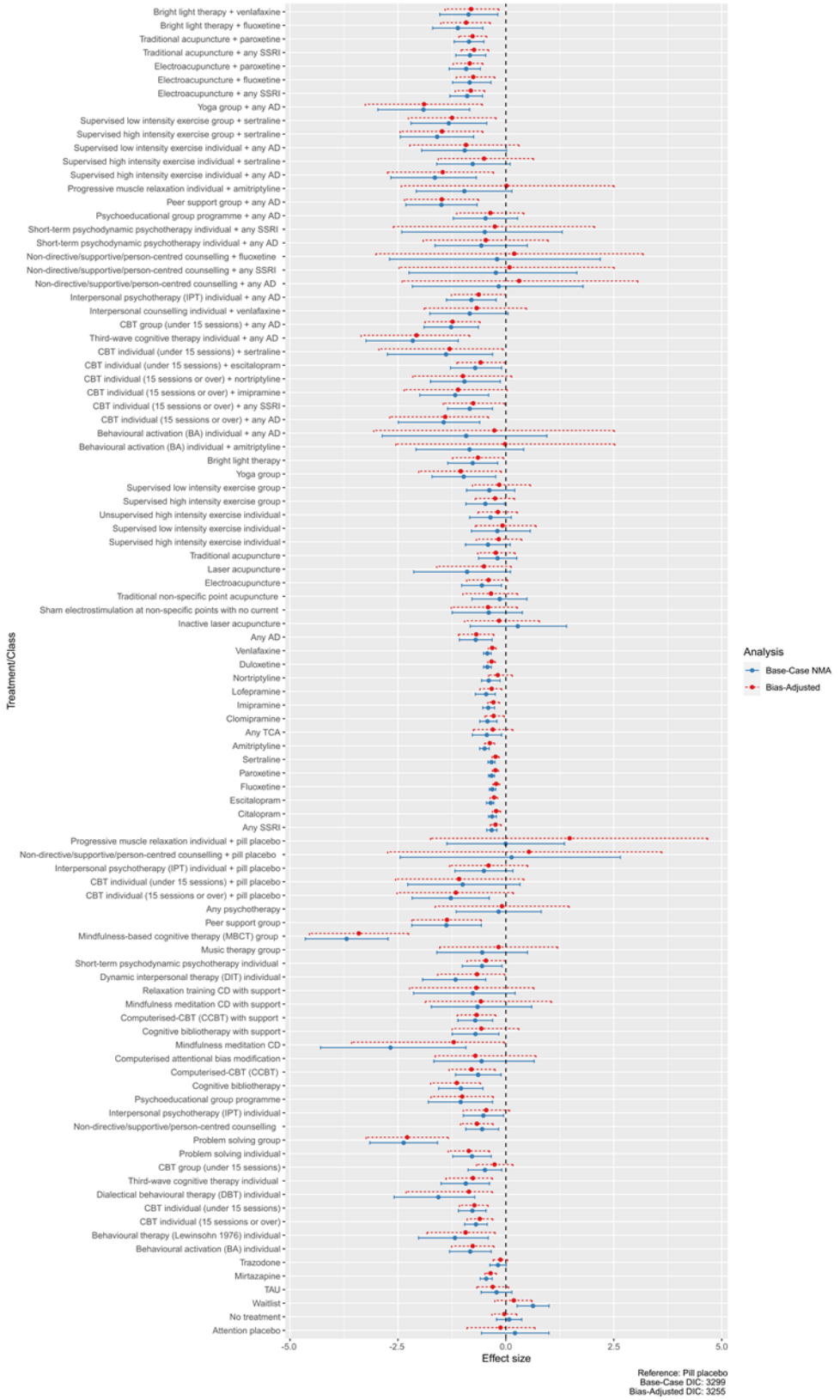
Although differences in estimates between the bias-adjusted and base-case models were smaller for classes, the change led to less clear evidence of efficacy versus TAU for the following classes in the bias-adjusted model compared to the base-case model (Figure 128):

- Cognitive and cognitive behavioural therapies individual
- Any AD
- Exercise group + AD
- Yoga group + AD

However, the direction of change in relative effects between the two models was less consistent for classes than for interventions.

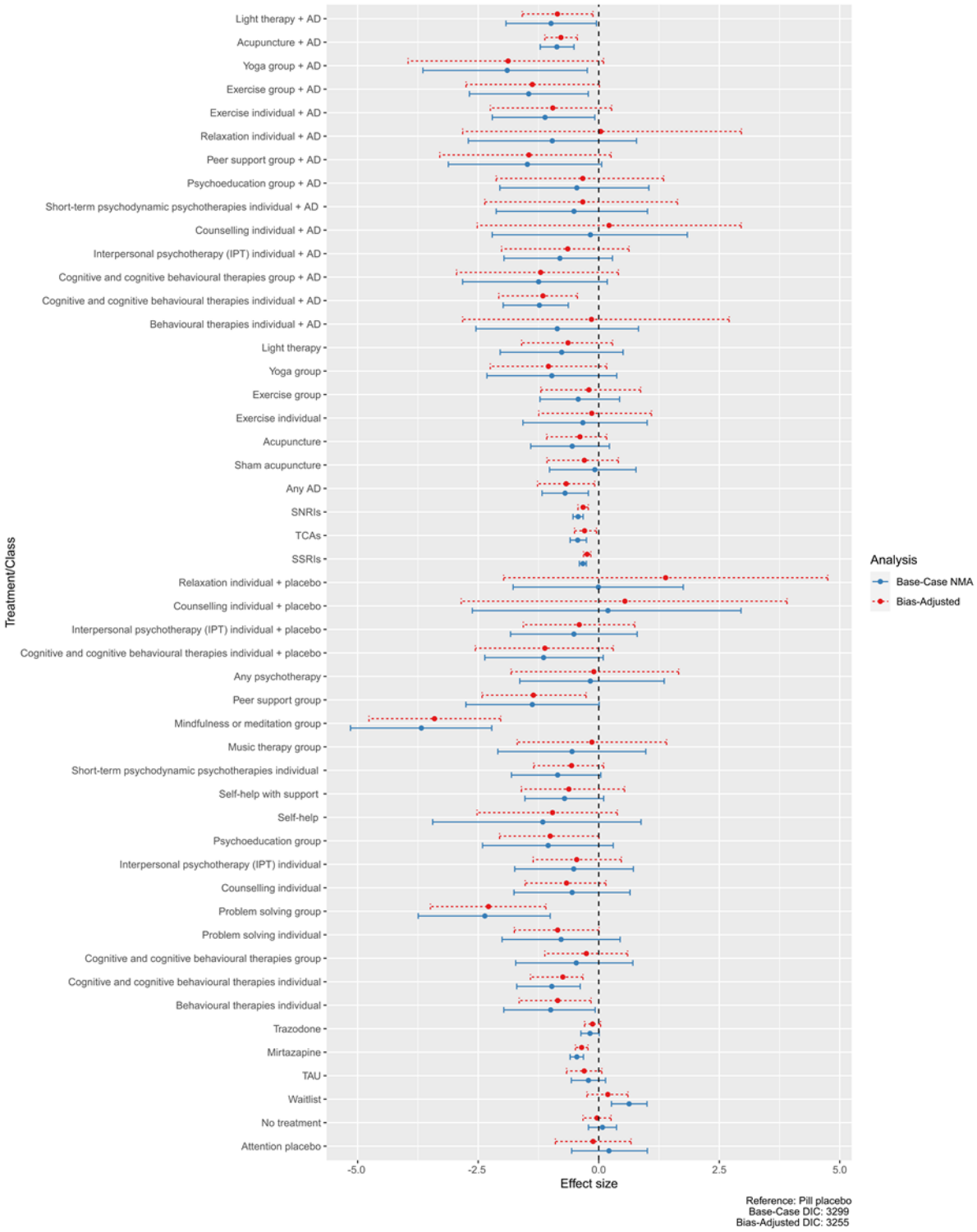
The posterior mean residual deviance, DIC and between study heterogeneity was substantially reduced compared to the base-case consistency model (supplement B5, Table 3.14 in Appendix 3). Reported results are therefore based on the bias-adjusted random-effects NMA model.

Figure 127: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each intervention versus pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, and bias-adjusted results by a short-dashed red line.

Figure 128: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each class versus pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results are indicated by a solid blue line, and bias-adjusted results by a short-dashed red line.

Sensitivity analyses: post-hoc

In addition to the pre-specified sensitivity analysis several post-hoc sensitivity analyses were performed to explore aspects of the data and modelling process that may have impacted results. They are reported here narratively.

In addition to investigating small study effects using bias-adjusted models (see under '*Pre-specified sensitivity analyses*'), the impact of excluding studies with <15 participants in any arm, and studies with >5 points contribution to the residual deviance was examined in analyses of response in randomised participants in both less severe and more severe depression. Although in both analyses the random effects NMA model was a better fit for this data and heterogeneity was considerably lower, there were no substantial changes in treatment efficacy. Several interventions and classes were excluded as these were only informed by very small studies.

To investigate the additivity assumption of interventions administered in combination with TAU, a separate model was fitted to the analysis of SMD in more severe depression that relaxed this assumption. The model included an interaction term for studies in which TAU was given in all study arms, which allowed for a multiplicative effect of an intervention when given in combination with TAU. Although the posterior distribution for the interaction term was non-zero (0.47; 95%CrI: 0.16, 0.79), neither the DIC (3359 in the interaction model compared to 3362 in the base-case model) nor the between-study SD (0.26 in the interaction model compared to 0.26 in the base-case model) was meaningfully different, suggesting that the assumption of additivity was reasonable.

Although we reported the results of prespecified bias-adjusted sensitivity analyses that were intended to investigate the impact of small study effects likely to be related to risk of bias (see 'Sensitivity analyses: prespecified'), we also investigated performing subgroup analyses including only studies rated as "low risk" for different risk of bias domains.

For many domains, there were insufficient studies to analyse a low risk of bias subgroup. We conducted post-hoc sensitivity analyses in the subgroups of studies rated as low risk for attrition. Results for SMD in both less severe depression (Figure 129) and more severe depression (Figure 130) showed that results were very similar to those from the an NMA of the overall network. This suggested that bias from Attrition was unlikely to be an effect modifier in either analysis.

Figure 129. Standardised Mean Differences and 95% credible intervals on the SMD outcome in less severe depression for each class versus TAU from low risk of bias (attrition) subgroup and the overall network (base-case NMA).

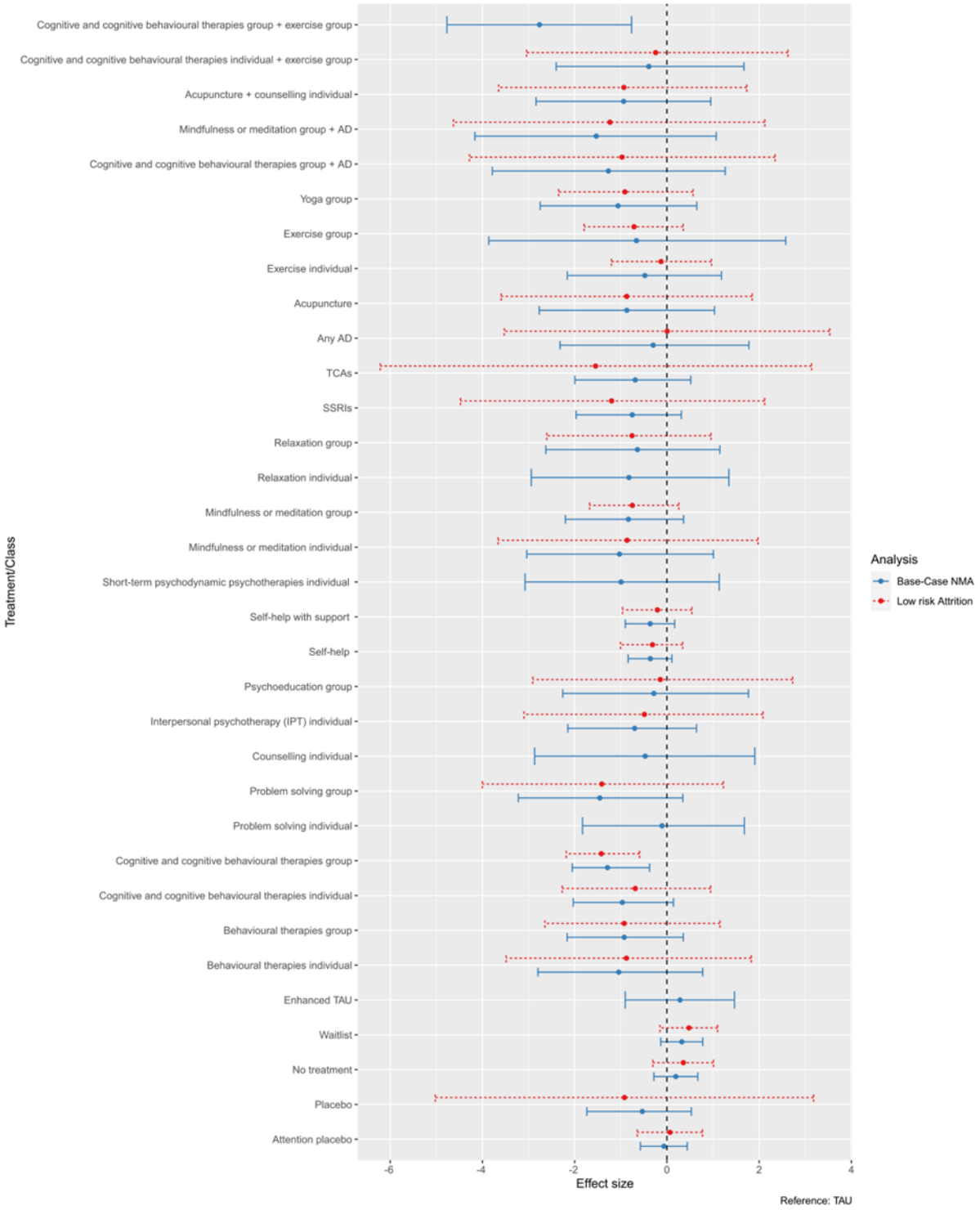
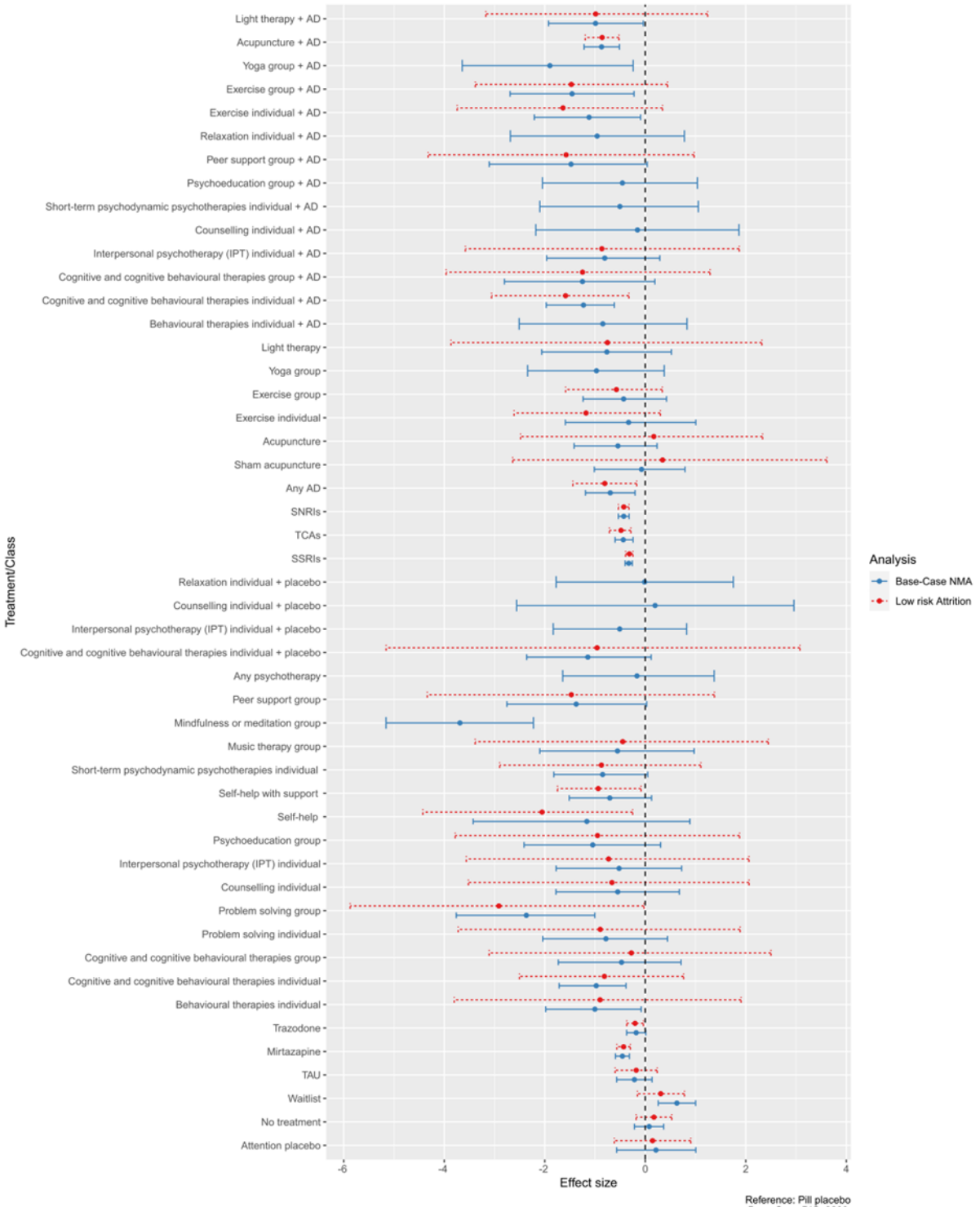


Figure 130. Standardised Mean Differences and 95% credible intervals on the SMD outcome in more severe depression for each class versus pill placebo from low risk of bias (attrition) subgroup and the overall network (base-case NMA).



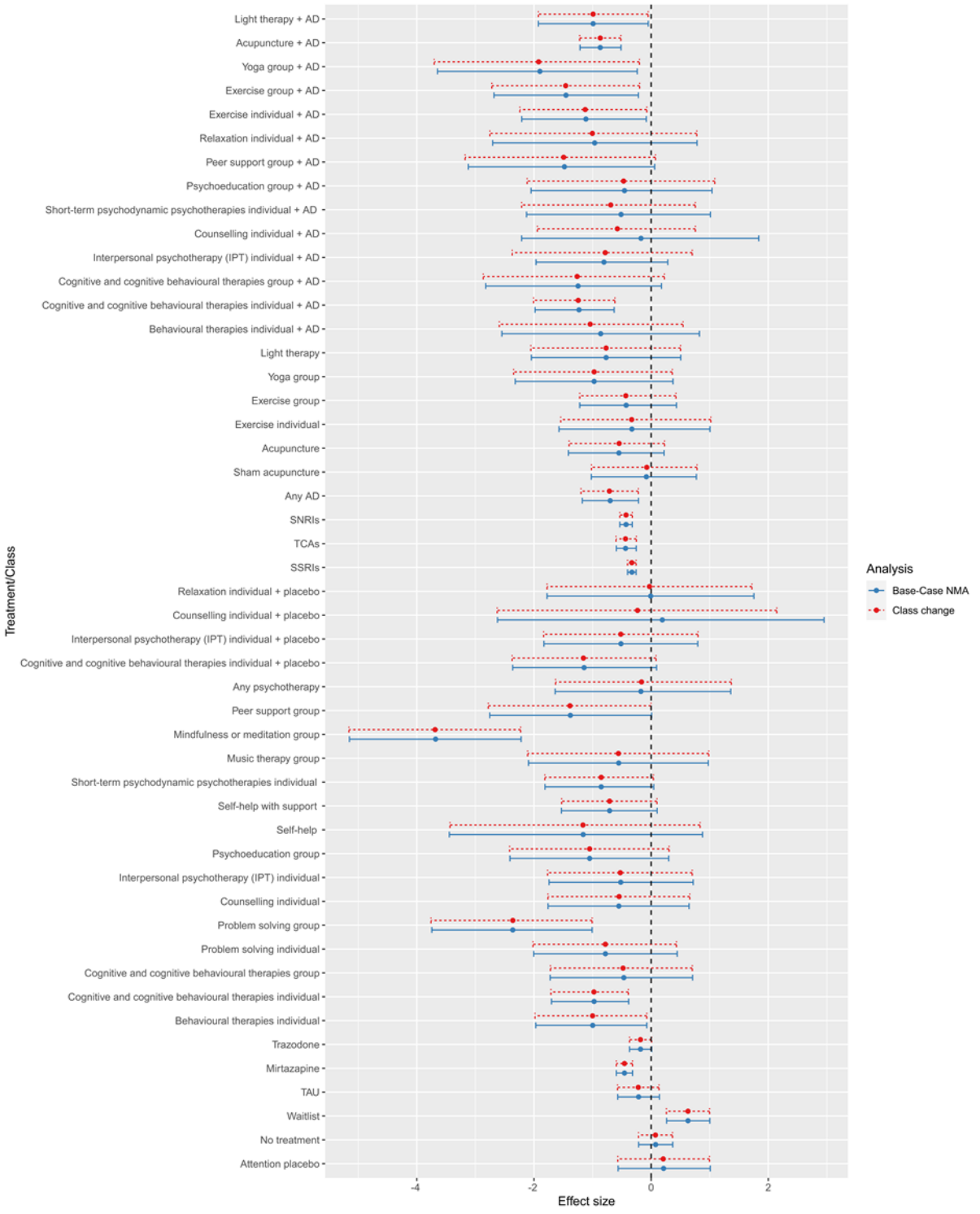
For Blinding (participants), Blinding (care administrator) and Performance, studies at low risk of bias are almost exclusively pharmacological studies, and the analysis is therefore equivalent to performing a subgroup analysis of pharmacological studies only. Given that we performed a prespecified sensitivity analysis of non-pharmacological studies only and found there was no meaningful impact on results, we would be unlikely to detect any differences that might arise from a subgroup of pharmacological only (equivalent to low risk of bias for Blinding or Performance).

Following the completion of the base-case analyses, it was identified that Interpersonal counselling + AD had been included in the class of Counselling + AD, when it was agreed by the Committee that it should be included in the class of Interpersonal psychotherapy (IPT) individual + AD. Although the class coding has been corrected for the main results presented for SMD in more severe depression, a sensitivity analysis was run to examine the impacts of this by fitting a model in which Interpersonal counselling + AD was included in the class of Counselling + AD. This led to (Figure 131):

- Substantially narrower 95%CrI for Counselling individual + AD versus Pill placebo, with a lower posterior median SMD (favouring Counselling individual + AD)
- Wider 95%CrI for Interpersonal psychotherapy (IPT) individual + AD versus Pill placebo, though the posterior median remained similar
- Substantially narrower 95%CrI for Counselling individual + Placebo versus Pill placebo, with a lower posterior median SMD (favouring Couselling individual + Placebo).

The changes would not have impacted conclusions and therefore the decision was taken to report the sensitivity analysis and retain the original (incorrect) class coding for all other outcomes.

Figure 131: Standardised Mean Differences and 95% credible intervals for symptom severity in more severe depression for each class versus Pill placebo.



Points indicate the posterior medians and horizontal error bars indicate the 95%CrIs. Base-case NMA results, in which Interpersonal counselling + AD was included in the class of Interpersonal counselling + AD, are indicated by a solid blue line. Results from the class change model, in which Interpersonal counselling + AD was included in the class of Counselling individual + AD, are indicated by a short-dashed red line.

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Appendix N – Resource use reported in the RCTs included in the network meta-analysis that informed the guideline economic analysis

Resource use in RCTs included in the network meta-analysis for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Table 138. Resource use reported in RCTs of psychological treatments for less severe depression included in the NMAs that informed the economic analysis.

Psychological treatments for less severe depression				
Study	**Duration (weeks)**	**Reported intended resource use (RCTs)**	**N**	**Delivered by**
Self-help (no support): computerised cognitive behavioural therapy (CBT)				
Christensen 2004a/ Mackinnon 2008	6	5 modules (29 exercises, actual 14.8)	182	Non-applicable
Dear 2018	5	4 modules	107	
de Graaf 2009/2011	8	8 x 30-min sessions (actual 3.4)	100	
Ebert 2018	7	6 modules (actual 5)	102	
Fitzpatrick 2017	2	12.14 check-ins	34	
Hur 2018	3	21x 10-15 min sessions	24	
Levin 2011	6	5 modules (mean use 258 min)	100	
Lintvedt 2013	8	5 modules	81	
Lobner 2018	6	5 modules	320	
McDermott 2019	6	6x 40-min sessions	144	
Melnyk 2015	10	7 modules	82	
Noguchi 2017	5	5 modules	326	
Powell 2013	6	5 modules	1534	
Rosso 2017	10	6 modules	37	
Self-help with support: computerised cognitive behavioural therapy (CBT) with support				
Dear 2018	5	4 modules (34.20 min therapist contact)	110	Psychologist
Geraedts 2014a/2014b	8	6 lessons	116	Master's students in clinical psychology
Ruwaard 2009	11	8 modules	36	graduate-level clinical psychologists /therapists
Sheeber 2017	16	8 modules (actual 6.6) + 8 coach calls (actual 6.9)	134	masters level therapist/bachelor level paraprofessional
Wagner 2014	8	7 modules	32	psychologist/psychotherapist
Behavioural therapies group: Behavioural activation (BA) group				
Vazquez 2020	5	5x 90-min sessions [actual mean 4]	70	Psychologist
Yang 2018	8	8 x 90 min sessions, 7-8 per group	37	Psychologist
Zemestani 2016	8	8x 90-min sessions	15	PhD student in psychology
Cognitive and cognitive behavioural therapies group: cognitive behavioural therapy (CBT) group <15 sessions				
Abdollahi 2017	12	12x 90-min sessions, 4-6 in group	35	Researcher (PhD in psychology)
Gordon 1987	14	14x 2-hour sessions	10	Nurse
Jones 2011	10	10x 90-min sessions	30	Principal investigator
Vazquez 2012	8	8x 90-min sessions, 5-6 in group	70	Clinical psychology PhD student
Vazquez 2016	5	5x 90-min sessions [actual 4.2], group of 5	88	Psychologist

Vazquez 2020	5	5x 90-min sessions [actual 4.4], 5 in group	69	Psychologist
Zemestani 2017	14	14x 90-min sessions	21	Doctoral students in psychology
Mindfulness or meditation group: mindfulness-based cognitive therapy (MBCT) group				
Asl 2014	8	8x 2-hour sessions	18	Not reported
Kitsumban 2009	4	11 sessions	30	Principal investigator
Lee 2010	8	8x 2.5-hour sessions	42	Clinical psychologist
Pots 2014	12	11x 45-min sessions, groups of 8-15	76	Psychologist/mental health nurse
Behavioural therapies individual: Behavioural activation (BA) individual				
Gawrysiak 2009	2	1x 90-min session	14	Doctoral students in clinical psychology
Luxton 2016 arm 1	8	8x 5-60 min sessions face-to-face	62	Doctoral-level mental health providers
Luxton 2016 arm 2	8	8x 5-60 min sessions over telephone	59	Doctoral-level mental health providers
McIndoo 2016	4	4x 1-hour sessions	16	Clinical psychology (doctoral) students
Taylor 2017	10	10x 1-hour sessions	16	Doctoral-level/master's level clinician
Yokoyama 2018	5	5x 1-hour sessions	19	Trained therapist
Cognitive and cognitive behavioural therapies individual: cognitive behavioural therapy (CBT) individual <15 sessions				
de Azevedo Cardoso 2014 arm 1	7	7x 1-hour sessions	60	Undergraduate psychology student
de Azevedo Cardoso 2014 arm 2	7	7x 1-hour sessions	60	Undergraduate psychology student
Fremont 1987	10	10x 1-hour sessions	19	Therapist (at least master's degree)
Gallagher-Thompson 2007	16	7x 90-min sessions	27	Not reported
Losada 2015	8	8x 90-min sessions	42	Clinical psychologist
Mondin 2014/2015 arm 1	7	7x 1-hour sessions	60	Senior psychology student
Mondin 2014/2015 arm 2	7	7x 1-hour sessions	60	Senior psychology student
Pace 1993	4-7	6-8 sessions [actual 7.39]	44	Graduate student in counselling
Wagner 2014	8	8 sessions	30	Psychologist/psychotherapist
Problem solving individual				
Kasckow 2014	16	6-8 sessions [actual 7]	25	Psychologist/psychiatrist/nurse
Kendrick 2005/2006a	8	6 sessions [actual 4.1]	90	Community mental health nurse
Lynch 1997	7	6x 20-min sessions	15	2nd year medical student or graduate nursing student
Rosen 2018	-	Not reported	29	Not reported
Non-directive counselling individual				
Friedli 1997	12	6-12x 50-min sessions (actual 7.7)	70	Therapist (with necessary qualifications and experience to be accredited by the British Association for Counselling)
Rosso 2013	26	15-30 sessions (actual 16.94)	55	Psychotherapist (psychiatrist/ psychologist/advanced supervised resident in psychiatry or clinical psychology)
Interpersonal psychotherapy (IPT) individual				
Beeber 2010	22	16 sessions	39	master's-prepared psychiatric nurses and project-trained Spanish language interpreters
Bernecker 2016	16	16 sessions	27	Psychologist/psychiatrist/doctoral-level psychology trainees (with at least a master's degree)
Van Schaik 2006	26	10 sessions (actual 8)	69	Psychologist/psychiatric nurse
Short-term psychodynamic psychotherapy individual				
Ajilchi 2016	NA	15 sessions	20	Psychologist
Rosso 2013	26	15-30 sessions (actual 18.61)	33	Psychotherapist (psychiatrist/ psychologist/ advanced

				supervised resident in psychiatry or clinical psychology)

Table 139. Resource use reported in RCTs of psychological treatments (alone or combined with antidepressants) for more severe depression included in the NMAs that informed the economic analysis.

Psychological treatments (alone or combined with antidepressants) for more severe depression				
Study	**Duration (weeks)**	**Reported intended resource use (RCTs)**	**N**	**Delivered by**
Self-help (no support): computerised cognitive behavioural therapy (CBT)				
Farrer 2011/Farrer 2012 arm 1	6	5 modules (actual 1.5)	38	Non-applicable
Farrer 2011/Farrer 2012 arm 2	6	5 modules (actual 2)	45	
Kay-Lambkin 2009	15	9 modules (actual 6.61)	32	
Kay-Lambkin 2011/2017	12	9x 1-hour sessions (actual 5.3)	97	
Self-help with support: computerised cognitive behavioural therapy (CBT) with support				
Alavi 2016	12	12 modules	47	Psychiatrist or psychiatry resident
Choi 2012	8	6 modules (actual 5.56); therapist time 97 min	32	Clinical psychologist or clinical psychology student (2nd year of doctoral training)
Hatcher 2018	12	Not reported	35	Coach (occupational therapy background)
Lindegaard 2019	8	7 modules (actual 4.4)	25	Master's degree-level students in clinical psychology
Thase 2018	16	9 modules (actual 8.1) + 12 therapist sessions (actual 11.0 sessions - 5 hrs)	77	Therapist (no further detail reported)
Vernmark 2010	8	7 modules (actual 6). Therapist time 53 mins per participant	29	Masters student
Vernmark 2010	8	7 modules; therapist time 509 min / participant	30	Masters student
Wright 2005	8	8 modules + 9 therapist sessions	15	Therapist (masters/doctoral level clinician)
Cognitive and cognitive behavioural therapies group: cognitive behavioural therapy (CBT) group <15 sessions				
Covi 1987	14	15x 2-hour sessions, group of 8	32	Psychiatrist & psychologist
Hamamci 2006	12	11x 1.5 hour sessions	10	Therapist
Husain 2014	12	10x 60-90 min sessions [actual 6.3], group of 11	33	Clinical psychologist & health visitor
Miranda 2003/2006	13	8 sessions	90	Psychotherapist
Sahranavard 2018	-	8x 90-min sessions	10	Masters degree level psychologist
Schmidt 1983 arm 1	8	8x 90 min sessions [actual 6.7], group of 5-6	11	Graduate paraprofessional therapist
Schmidt 1983 arm 2	8	8x 90min sessions [actual 6.7], group of 11	11	Graduate paraprofessional therapist
Thomas 1987	6	6 sessions, group of 5	15	Doctoral students in clinical psychology
Behavioural therapies individual: Behavioural activation (BA) individual				
Egede 2015	8	8x 1-hour sessions – same room	121	Masters-level counsellor
Egede 2015	8	8x 1-hour sessions - videoconferencing	120	Masters-level counsellor
Jacobson 1996	-	20 sessions	57	Clinical psychologist
Kanter 2015	12	12x 50-min sessions	21	Mental health practitioner
Moradveisi 2013	12	16 sessions	50	Counsellor psychologist
Patel 2017/Weobong 2017	12	6-8x 30-40 min sessions	247	Lay counsellor
Cognitive and cognitive behavioural therapies individual: cognitive behavioural therapy (CBT) individual ≥15 sessions				
Beach 1992	15	15-20 sessions	15	doctoral level psychologist or advanced graduate student in clinical psychology
Blackburn 1981	12-20	15-23 sessions [actual 15.3]	22	Clinical psychologist
Blackburn 1997	16	16 sessions	27	Clinical psychologist
Bulmash 2009	16	16 sessions	37	Psychologist (master's in social work or PhD)

Connolly Gibbons 2016	22	16 sessions	119	Clinician (masters degree or above)
Elkin 1989/Imber 1990	16	16-20x 50-min sessions [average 13]	62	Psychologist/psychiatrist
Fonagy 2019	16-24	14-18x 1-hour sessions	20	Trained CBT practitioner (within IAPT)
Gallagher-Thompson 1994	16	20 sessions	36	Therapist (masters degree in social work or PhD-level psychologists)
Hautzinger 1996	8	24x 50-60 min sessions	40	Clinical psychologist
Hollon 1992	12	Max 20x 50-min sessions [actual 14.9]	25	Clinical psychologist or clinical social worker
Jacobson 1996 arm 1	-	20 sessions	44	Clinical psychologist
Jacobson 1996 arm 2	-	20 sessions	50	Clinical psychologist
Kennedy 2007	16	16 sessions [actual 14.1]	17	Trained CBT therapist
Marshall 2008	16	16 sessions	37	Doctoral-level or postdoctoral clinical psychology student
Mohr 2011	20	16x 45-50 min sessions	41	Clinical psychologist
Murphy 1984	12	20x 50-min sessions [actual 17.1]	19	Psychologist/psychiatrist
Quilty 2014	16	16 sessions	49	Psychologist/doctoral trainee
Rosner 1999	20	20 sessions	18	Psychologist/psychiatrist
Rush 1977/Kovacs 1981	12	20x 50-min sessions [actual 15.3]	19	Psychiatric resident, post- or pre-doctoral clinical psychologist/psychiatrist
Thase 2018	16	20x 50-min sessions [actual 16]	77	Therapist (no further detail)
Zu 2014	24	20x 1-hour sessions	30	Clinical psychologist
Problem solving individual				
Alexopoulos 2003b	12	12 sessions	12	Therapist (no further detail)
Arean 2010	12	12 sessions	110	Doctoral-level clinical psychologist/licensed social worker
Choi 2014a/Choi 2014b arm 1	12	6x 1-hour sessions	42	Licensed master's-level social workers
Choi 2014a/Choi 2014b arm 2	12	6x 1-hour sessions	43	Licensed master's-level social workers
Kramer 2014	9	5x 1-hour sessions [actual 1.36]	131	Healthcare professional
Mynors-Wallis 1995	12	6x 30-60 min sessions	30	GP or psychiatrist
Mynors-Wallis 2000 arm 1	12	6x 30-60 min sessions [actual 4.6]	39	GP
Mynors-Wallis 2000 arm 2	12	6x 30-60 min sessions [actual 4.6]	41	Nurse
Non-directive counselling individual				
Alexopoulos 2003b	12	12 sessions	13	Therapist (no further detail)
Arean 2010	12	12 sessions	111	Doctoral-level clinical psychologist/licensed social worker
Bedi 2000/Chilvers 2001	8	6 sessions	52	Counsellor (at least 2000 hours of supervised experience or attached to primary care team)
Kay-Lambkin 2011/2017	12	9x 1-hour sessions [actual 5.4]	89	Therapist
Markkula 2019	4	5x 45-min sessions [actual 5.2]	141	Lay counsellor
Ward 2000/King 2000	16	6-12x 50-min sessions [actual 6.4]	67	Counsellors (accredited by British Association for Counselling)
Interpersonal psychotherapy (IPT) individual				
Blom 2007	12	12 sessions	34	Therapist (no further detail)
Bulmash 2009	16	16 sessions	42	Psychologist (master's in social work or PhD level)
Elkin 1989/Imber 1990	16	16-20x 50-min sessions (actual 13)	63	Psychologist/psychiatrist
Marshall 2008	16	16 sessions	35	Doctoral-level or postdoctoral clinical psychology students
Short-term psychodynamic psychotherapy individual				
Connolly Gibbons 2012	12	12x 1-hour sessions (actual 7.4)	21	Therapist with master's degree in a mental health field

Connolly Gibbons 2016	22	16 sessions	118	Clinician (masters degree or above)
Gallagher-Thompson 1994	16	20 sessions	30	Therapist (masters degree in social work/PhD-level psychologists)
Salminen 2008	16	16 sessions	26	Psychiatrist/psychologist
Cognitive and cognitive behavioural therapies individual + antidepressant: cognitive behavioural therapy (CBT) individual ≥15 sessions + antidepressant				
Ashouri 2013	-	Not reported	10	PhD student of Clinical Psychology
Blackburn 1981	12-20	15-23 sessions (actual 14.6)	22	Clinical psychologist
Hautzinger 1996	8	24x 50-60 min sessions	38	Clinical psychologist
Hollon 1992	12	Max of 20 x 50-min sessions (actual 14.9)	25	Clinical psychologist or clinical social worker
Klieser 1988 arm 1	3	21x 20-min sessions	12	NR
Klieser 1988 arm 2	3	21x 20-min sessions	11	NR
Murphy 1984	12	20x 60-min sessions (actual 16.17)	18	Psychologist
Zu 2014	24	20x 1-hour sessions	60	Clinical psychologist

Table 140. Resource use reported in RCTs of physical treatments for less severe depression included in the NMAs that informed the economic analysis.

Physical treatments for less severe depression				
Study	**Duration (weeks)**	**Reported intended resource use (RCTs)**	**N**	**Delivered by**
Exercise individual: supervised high intensity individual exercise				
Doyne 1987	8	32 sessions [actual 21.12]	14	Undergraduate exercise monitor
Legrand 2014	7	14x 1-hour sessions [some were delivered in groups of 80]	22	Exercise instructor
Sims 2006	10	30 sessions	17	Not reported
Exercise group: supervised high intensity group exercise				
Alsaraireh 2017	10	30x 1-hour sessions	100	Not reported
Balchin 2016	6	36x 1-hour sessions	11	Not reported
Brenes 2007	16	48x 1-hour sessions	14	Certified American College of Sports Medicine exercise leader
Fremont 1987	10	30 sessions, 6-8 per group	21	Running coach
Singh 1997a/1997b	10	30x 50-min sessions, 1-8 per group	17	Principal investigator

Table 141. Resource use reported in RCTs of physical treatments (alone or combined with antidepressants) for more severe depression included in the NMAs that informed the economic analysis.

Physical treatments (alone or combined with antidepressants) for more severe depression				
Study	**Duration (weeks)**	**Reported intended resource use (RCTs)**	**N**	**Delivered by**
Acupuncture: traditional acupuncture				
Allen 2006	8	12 sessions	53	Trained & board certified acupuncturist
Du 2005	6	42 sessions	78	Not reported
Fu 2003	8	16x 30-min sessions	32	Not reported
Fu 2008	12	24x 30-min sessions	NA	Not reported
Jiahui 2006	4	30 sessions	30	Not reported
Li 2004b	6	30 sessions	49	Not reported
Pei 2006	6	30x 30-min sessions	62	Not reported
Zhang 2005	6	30-40 sessions	43	Not reported
Zhang 2007b	4	28 sessions	50	Not reported
Exercise individual: Supervised high intensity exercise individual				

Blumenthal 1999/Babyak 2000	16	48x 45-min sessions	53	Not reported
Dunn 2005 arm 1	12	60 sessions	17	Laboratory staff
Dunn 2005 arm 2	12	36 sessions	16	Laboratory staff
Gerber 2020	6	18 sessions	20	Not reported
Hemat-Far 2012	8	24x 40-60-min sessions	10	Not reported
Huipeng 2013	6	30 sessions	35	Not reported
Jinchun 2015	8	40 sessions	35	Not reported
Krogh 2012	12	36x 45-min sessions (actual 13.5)	56	Physiotherapist
Khoshnab 2017	8	24x 40-60 min sessions	15	Not reported
Exercise group: Supervised high intensity exercise group				
Blumenthal 2007/Hoffman 2011	16	48x 45-min sessions (median 37)	51	Not reported
Guifeng 2015	8	40 sessions	35	Not reported
Herman 2002	16	48x 45-min sessions (median 43)	53	Not reported
Klieser 1988	3	21x 20-min sessions	11	Not reported
Singh 2005	8	24x 65-min sessions, in groups of 1-8	20	Not reported
Acupuncture + AD: traditional acupuncture + SSRI				
Ai 2018	6	42 x 50-min sessions	50	Not reported
Qu 2013	6	18 sessions	54	Acupuncturist
Wang 2014a	6	30 sessions	48	Acupuncturist
Xu 2011	6	18 sessions	NA	Not reported
Zhao 2019a	6	18 x 30-min sessions	161	Acupuncturist