National Institute for Health and Care Excellence

Final

Attention deficit hyperactivity disorder (update)

[F] Evidence review for combined pharmacological and non-pharmacological treatments review

NICE guideline NG87

Intervention evidence review

March 2018

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

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

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1 Combined pharmacological and non-pharmacological treatments

1.1 Review question: What is the most clinically and cost-effective combination of pharmacological and non-pharmacological treatment for people with ADHD?

1.2 Introduction

Combining medication and non-pharmacological therapy has the potential to increase effectiveness compared with one treatment alone. In people with ADHD combining treatments may increase effects on core ADHD symptoms through the interaction of the two approaches. The potential value of combining medication and non-pharmacological therapy for people with ADHD might lead to beneficial effects in different domains. For example, medication targeting the core ADHD symptoms such as inattention and hyperactivity/impulsivity, and psychosocial interventions targeting secondary problems and coexisting conditions associated with ADHD. Combining pharmacological and non-pharmacological approaches may also have the potential to deliver both immediate effects on ADHD symptoms through medication, along with more long-lasting effects through the development of behavioural and cognitive skills and strategies. This review evaluates the evidence on the use of combined interventions where medication and non-pharmacological therapies are used together to treat ADHD and while the two approaches are complimentary head to head comparisons between the two are evaluated.

This review should be read alongside evidence review C on pharmacological efficacy and sequencing, evidence report D on pharmacological safety and evidence report E on non-pharmacological efficacy and adverse events.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Children, young people and adults with ADHD. Stratified by age: • Under 5 years • 5 to 18 years • Over 18 years
Intervention(s)	Pharmacological treatments (mixed, stimulants [including methylphenidate, dexamfetamine and lisdexamfetamine], atomoxetine, guanfacine) Non-pharmacological treatments (parent/family/carer training, cognitive behavioural therapy (CBT), Dialectical behaviour therapy (DBT), psychoeducation, attention/memory/cognitive training, neurofeedback, relaxation techniques, organisational skills/school or workplace targeted interventions, exercise, outdoor activities, non-specific supportive therapy (NSST)) Combinations of pharmacological and non-pharmacological treatments
Comparison(s)	Any pharmacological treatment versus any non-pharmacological treatment Any combined treatment versus any pharmacological/non-pharmacological treatment alone

	Any combined treatment versus any other combined treatment Any combined treatment versus usual care
Outcomes	• Quality of life • ADHD symptoms (total, inattention, hyperactivity, stratified by rater) • Discontinuation due to intervention • Serious adverse events • Behavioural measures • Emotional dysregulation • Academic outcomes
Study design	RCTs only

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[46] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Evidence was divided into the following categories:

- Non-pharmacological treatments versus pharmacological treatments
- Combined treatments versus non-pharmacological treatments
- Combined treatments versus pharmacological treatments
- Combined treatments versus no treatment/treatment as usual
- Combined treatments versus any other combined treatment

Studies were not included if they systematically selected a population who were responders to the primary treatment under investigation (for example a population of only responders to methylphenidate randomised to CBT alone or CBT with methylphenidate).

Evidence was separated into short term (under 3 months) and longer term (greater than 3 months. Evidence was also separated into whether the outcomes were assessed at the end of treatment (post-treatment (PT)) or at the end of a follow-up period beyond the treatment (follow-up (FU)).

A network meta-analysis was considered for this question but deemed inappropriate due to concerns over differences in trial populations, exact trial interventions and insufficient data available for the relevant outcomes (see the methodology chapter for further details). Although it was not deemed appropriate to conduct an NMA across the entirety of the clinical review, in order to pragmatically obtain the best possible evidence for the select areas in which health economic modelling was feasible and a high priority, a more restricted NMA was conducted. Please see Appendix 3 for more information

1.5 Clinical evidence

1.5.1 Included studies

Thirty-three studies (in 35 publications) were included in the review; [1,3,9-13,17,20,21,24,26,28,34,36-38,41,43,44,49-52,54-56,59,61-63,65-68] these are summarised in Table 2 and Table 3 below. Evidence from these studies is summarised in the clinical evidence summary tables below.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

There were 0 studies in the under 5 year old category 23 studies in the 5 to 18 year old category and 10 studies in >18 year old category.

The majority of studies (n=23) compared combination to pharmacological interventions, 13 compared combination to non-pharmacological interventions, 8 compared pharmacological to non-pharmacological, 4 compared combination to usual care and 1 compared combination to another combination.

A number of studies included more than two arms and therefore contributed to more than one comparison.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review for children aged over 5 to 18

Study	Intervention and comparison	Population	Outcomes	Comments
Abikoff 2004[3]	Stimulants alone (n = 34), 12 months Stimulants + parent/family training (n = 34), 12 months Stimulants + non-specific supportive therapy (n = 35), 12 months Follow-up to 2 years	Aged 7 to 9.9 (mean 8.2) Participants were all selected as responders to 5 weeks of open label methylphenidate USA	ADHD symptoms	General ADHD population
Dose 2016[9]	Stimulants + parent/family training (n = 51) Stimulants (n = 52) Follow-up and intervention duration 12 months	Aged 6 to 12 Participants were previously using drugs for ADHD and not responding Germany	ADHD symptoms Behaviour/function	General ADHD population Parent/family training predominantly delivered via mailed self-help manuals with telephone follow-up
Duric 2014[10]	Stimulants + neurofeedback (n = 22) Stimulants (n = 27)	Aged 6 to 17 (mean 11.5) Not selected based on previous	ADHD symptoms Academic	General ADHD population

Study	Intervention and comparison	Population	Outcomes	Comments
	Neurofeedback (n = 24) Follow-up (estimated intervention duration) 10 weeks	treatment or response Norway		
Duric 2017[11]	Stimulants + neurofeedback (n =44), 3 months Stimulants (n =42), 3 months Neurofeedback (n =42), 3 months Follow-up 6 months	Aged 6 to 18 (mean 11.2) Not selected based on previous treatment or response Norway	ADHD symptoms Academic	General ADHD population
Ferrin 2014[17]	Mixed medication + psychoeducation (n = 40), 12 weeks Mixed medication + non-specific supportive therapy (n = 36), 12 weeks Follow-up to 15 months	Aged 3 to 19 (mean 10.65) Not selected based on previous treatment or response Spain	ADHD symptoms Behaviour/ function Emotional dysregulation	General ADHD population
Gelade 2016[20]	Stimulants (n = 33) Exercise (n = 37) Follow-up and intervention duration to 10-12 weeks	Mean age 9.63 (SD 1.76) All were free of stimulant use for at least 1 month Netherlands	ADHD symptoms	General ADHD population
Handen 2015[21]	Atomoxetine + parent/family training (n = 32) Atomoxetine (n = 32) Parent/family	Aged 5 to 14 (mean age 8.1) USA	ADHD symptoms Responders by CGI-I	ADHD and ASD

Study	Intervention and comparison	Population	Outcomes	Comments
	training (n = 32) Placebo/usual care (n = 32) Follow-up and intervention duration 10 weeks			
Hiscock 2015[24]	Mixed medication + sleep intervention (n = 122) Mixed medication (n = 122) Follow-up and intervention duration 6 months	Aged 5 to 12 years Not selected based on previous treatment or response Australia	ADHD symptoms Behaviour/function	General ADHD population
Lee 2017[36]	Mixed medication + neurofeedback (n = 18) Mixed medication (n = 18) Follow-up and intervention duration 10 weeks	Mean age 8.7 (SD 2) Not selected based on previous treatment or response South Korea	ADHD symptoms Behaviour/function	General ADHD population
Li 2013[38]	Stimulants + neurofeedback (n = 31), 8-20 weeks Stimulants + attention training (n = 29), 8-20 weeks Follow-up to 6 months	Mean age 10.6 (SD 2.8) Not selected based on previous treatment or response China	ADHD symptoms	General ADHD population
MTA study 1999[1,28]	Mixed medication + parent/family training (n = 134), 14 months Mixed medication (n = 120), 14 months Parent/family training (n = 129), 14 months Waitlist/usual care	Mean age 8.5 (SD 0.8) Not selected based on previous treatment or response USA	ADHD symptoms Academic	General ADHD population

Study	Intervention and comparison	Population	Outcomes	Comments
	(n = 128) Follow-up to 3 years			
Merrill 2016[41]	Mixed medication + parent/family training (n = 39) Parent/family training (n = 36) Mixed medication (n = 36) Waitlist/usual care (n = 36) Follow-up and intervention duration 2 months	Mean age 8 (SD 1.7) Not selected based on previous treatment or response USA	Academic	General ADHD population
Mohammadi 2014[43]	Stimulants + attention/memory/ cognitive training (n = 23) Stimulants (n = 25) Follow-up to ~2 months	Age range from 6 to 12 Not selected based on previous treatment or response Iran	ADHD symptoms	General ADHD population
Montoya 2014[44]	Mixed medication + parent/family training (n = 144) Mixed medication (n = 126) Follow-up to 12 months (intervention duration unclear)	Mean age 9.1 (SD 1.9) Participants were pharmacologically naïve Spain	ADHD symptoms	General ADHD population
Riggs 2011[50]	Stimulants + CBT (n = 151) CBT (n = 152) Follow-up and intervention duration 4 months	Mean age 16.5 (SD 1.3) Participants had not used psychotropic medication in previous month USA	ADHD symptoms	Majority moderate severity Comorbid non-tobacco substance use disorder
So 2008[54]	Stimulants + parent/family training (n = 45)	Mean age 8.0 (SD 0.9)	ADHD symptoms	General ADHD population

Study	Intervention and comparison	Population	Outcomes	Comments
	Stimulants (n = 31) Follow-up to 18 months	Participants were pharmacologically naïve Hong Kong		
Sprich 2016[55]	Mixed medication + CBT (n = 46), 6 months Mixed medication (n = 46), 6 months Follow-up to 1 month	Mean age 15.13 (SD 1.1) Participants were previously using drugs for ADHD and not responding USA	ADHD symptoms	General ADHD population
Storebo 2012[56]	Mixed medication + parent/family training (n = 28) Mixed medication (n = 27) Follow-up and intervention duration 6 months	Age range 8 to 12 Participants were pharmacologically naïve Denmark	ADHD symptoms Behaviour/function Emotional dysregulation Academic	General ADHD population
Svanborg 2009[59]	Atomoxetine + psychoeducation (n = 49) Psychoeducation (n = 50) Follow-up and intervention duration 10 weeks	Age range 6 to 15 Participants were pharmacologically naïve Sweden	Quality of life ADHD symptoms Academic	General ADHD population
Thurstone 2010[61]	Atomoxetine + CBT (n = 32) CBT (n = 33) Follow-up and intervention duration 3 months	Mean age 16.1 (SD 1.6) Not selected based on previous treatment or response USA	ADHD symptoms Responders by CGI-I	Comorbid non-tobacco substance use disorder
Van der Oord[62]	Stimulants + parent/family training (n = 24) Stimulants (n = 21)	Mean age 9.9 (SD 1.2) Participants were pharmacologically naïve	ADHD symptoms	General ADHD population

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up and intervention duration 10 weeks	Netherlands		
Vidal 2015[63]	Mixed medication + CBT (n = 59) Mixed medication (n = 60) Follow-up and intervention duration to ~3 months	Mean age 17.47 (SD 1.88) Participants were previously treated with ADHD medication, response not specified Spain	ADHD symptoms	General ADHD population
Waxmonsky 2010[65]	Atomoxetine + parent/family training (n = 29) Atomoxetine (n = 27) Follow-up and intervention duration 2 months	Mean age 8.59 (SD 1.58) Not selected based on previous treatment or response USA	ADHD symptoms Responders by CGI-I Behaviour/function	General ADHD population

Table 3: Summary of studies included in the evidence review for adults

Study	Intervention and comparison	Population	Outcomes	Comments
Emilsson 2011[12]	Mixed medication + CBT (n = 15), 8 weeks Mixed medication (n = 17), 8 weeks Follow-up to ~5 months	Mean age 33.88 (SD 11.47) Participants were previously treated with ADHD medication, with persistent symptoms Iceland	ADHD symptoms	General ADHD population
Estrada 2013[13]	Mixed medication + CBT (n = 15) Mixed medication + non-specific supportive therapy (n = 17) Follow-up and intervention	Mean age 39.47 (SD 7.68) Participants were previously treated with ADHD medication, partially responsive	Quality of life ADHD symptoms Emotional dysregulation	General ADHD population

Study	Intervention and comparison	Population	Outcomes	Comments
	duration 3 months	Spain		
Jans 2015[26]	Stimulants + CBT + parent/family training (n = 77) Non-specific supportive therapy + parent/family training (n = 66) Follow-up and intervention duration 1 year	Mean age 38.32 (SD 5.69) Participants were not previously treated with methylphenidate or psychotherapy Germany	ADHD symptoms (maternal) ADHD symptoms (child) Emotional dysregulation	Mothers with ADHD, with children with ADHD (treatment aimed at mothers) Both groups received parent/family training after a period of either stimulant and CBT treatment or non-specific supportive treatment
Konstenius 2014[34]	Stimulants + CBT (n = 27) CBT (n = 26) Follow-up and intervention duration 6 months	Mean age 41.5 (SD 9.83) Not selected based on previous treatment or response Sweden	ADHD symptoms	Participants from medium security prisons with comorbid amphetamine dependence
Levin 2007[37]	Stimulants + CBT (n = 53) CBT (n = 53) Follow-up and intervention duration 14 weeks	Mean age 37 (SD 6.5) Not selected based on previous treatment or response USA	ADHD symptoms Responders by CGI-I	Comorbid cocaine dependence
Philipsen 2015[49]	Stimulants + CBT (n = 103) Stimulants + non-specific supportive therapy (n = 110) Placebo + CBT (n = 107) Placebo + non-specific supportive therapy (n = 103) Follow-up and intervention	Mean age 35 (SD 10.26) Participants had not used stimulants for ADHD or psychotherapy aimed at ADHD in preceding 6 months Germany	ADHD symptoms Emotional dysregulation	General ADHD population

Study	Intervention and comparison	Population	Outcomes	Comments
	duration 1 year			
Safren 2005[51]	Mixed medication + CBT (n = 16) Mixed medication (n = 15) Follow-up and intervention duration 15 weeks	Mean age 45.5 (SD 10.6) Participants were previously using ADHD medication and responsive but with persistent symptoms USA	ADHD symptoms Emotional dysregulation	General ADHD population
Safren 2010[52]	Mixed medication + CBT (n = 38), 15 weeks Mixed medication + non-specific supportive therapy (n = 32), 15 weeks Follow-up to ~18 months	Mean age 43.2 (SD 11.3) Participants were previously using medication for ADHD and had persistent symptoms USA	ADHD symptoms CGI-I responders	General ADHD population
Weiss 2012[66]	Stimulants + CBT (n = 23), 14 weeks CBT (n = 25) Follow-up to 5 months, 14 weeks	Mean age 35.6 (SD 9.9) Not selected based on previous treatment or response USA and Canada	ADHD symptoms Responders by CGI-I Emotional dysregulation	General ADHD population
Young 2015[67,68]	Mixed medication + CBT (n = 25) Mixed medication (n = 32) Follow-up and intervention duration 3 months	Mean age 35.2 (SD 11.7) Previously on medication for ADHD, response not specified Iceland	Quality of life ADHD symptoms Emotional dysregulation Behaviour/ function	General ADHD population

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

1.5.4.1 Children and young people aged 5 to 18

1.5.4.1.1 Pharmacological treatment versus non-pharmacological treatment in children and young people

Table 4: Clinical evidence summary: Atomoxetine versus parent/family training

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PT/FT	Risk difference with Atomoxetine (95% CI)
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.45	The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.21 lower (0.5 lower to 0.08 higher)
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.46	The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.03 higher (0.35 lower to 0.41 higher)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.44	The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.32 lower (0.68 lower to 0.04 higher)
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias,		The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, higher is worse, fv, pt <3	The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, higher is worse, fv, pt <3

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PT/FT	Risk difference with Atomoxetine (95% CI)
		imprecision		months) in the control groups was 1.28	months) in the intervention groups was 0.04 higher (0.43 lower to 0.51 higher)
ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.45	The mean ADHD symptoms (inattention, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.09 lower (0.41 lower to 0.23 higher)
ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.64	The mean ADHD symptoms (inattention, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.02 higher (0.37 lower to 0.41 higher)
Responders by CGI-I (PT, <3 months)	63 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.61 (0.83 to 3.13)	290 per 1000	177 more per 1000 (from 49 fewer to 618 more)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.

Table 5: Clinical evidence summary: Stimulants versus exercise

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Exercise	Risk difference with Stimulants (95% CI)
ADHD symptoms (hyperactivity, parent, SWAN, 0-3, high is poor, FV, PT <3 months)	73 (1 study) 10-12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, swan, high is poor, fv, pt <3 months) in the control groups was 1.07	The mean ADHD symptoms (hyperactivity, parent, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.45 lower (0.84 to 0.06 lower)
ADHD symptoms (hyperactivity, teacher, SWAN,0-3, high is poor, FV, PT <3 months)	70 (1 study) 10-12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, swan, high is poor, fv, pt <3 months) in the control groups was 1.1	The mean ADHD symptoms (hyperactivity, teacher, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.87 lower (1.3 to 0.44 lower)
ADHD symptoms (inattention, parent, SWAN, 0-3, high is poor, FV, PT <3 months)	73 (1 study) 10-12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, swan, high is poor, fv, pt <3 months) in the control groups was 1.11	The mean ADHD symptoms (inattention, parent, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.50 lower (0.86 to 0.14 lower)
ADHD symptoms (inattention, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)	70 (1 study) 10-12 weeks	MODERATE[a] due to risk of bias		The mean ADHD symptoms (inattention, teacher, swan, high is poor, fv, pt <3 months) in the control groups was 1.33	The mean ADHD symptoms (inattention, teacher, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.76 lower (1.12 to 0.4 lower)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.

Table 6: Clinical evidence summary: Stimulants versus Neurofeedback

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with NF	Risk difference with Stimulants (95% CI)
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, <3 months) in the control groups was 23.5	The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 4.60 higher (0.46 to 8.74 higher)
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,c] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, >3 months) in the control groups was 23.8	The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.30 lower (5.21 lower to 4.61 higher)
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 21	The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 2.70 higher (2.93 lower to 8.33 higher)
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 25.3	The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.80 higher (4.45 lower to 6.05 higher)
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, <3 months) in the control groups was 9.2	The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 3.00 higher (0.49 to 5.51 higher)
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias,		The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, >3	The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, >3 months) in

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants (95% CI)
		imprecision		months) in the control groups was 10	the intervention groups was 1.40 higher (1.43 lower to 4.23 higher)
ADHD symptoms (hyperactivity, parent, SWAN, 0-3, high is poor, FV, PT <3 months)	75 (1 study) 10-12 weeks	LOW[b,d] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, swan, high is poor, fv, pt <3 months) in the control groups was 1.02	The mean ADHD symptoms (hyperactivity, parent, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.40 lower (0.79 to 0.01 lower)
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 10.8	The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 0.40 higher (3.33 lower to 4.13 higher)
ADHD symptoms (hyperactivity, teacher, Barkley's,0-54, high is poor, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 10.5	The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 2.50 higher (0.59 lower to 5.59 higher)
ADHD symptoms (hyperactivity, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)	72 (1 study) 10-12 weeks	LOW[b,d] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, swan, high is poor, fv, pt <3 months) in the control groups was 1.16	The mean ADHD symptoms (hyperactivity, teacher, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.93 lower (1.39 to 0.47 lower)
ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months)	52 (1 study) <3 months	VERY LOW[a,c] due to risk of bias,		The mean ADHD symptoms (hyperactivity, self, srq, 1-10, high is good, cs, pt <3 months)	The mean ADHD symptoms (hyperactivity, self, srq, 1-10, high is good, cs, pt <3 months)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants (95% CI)
		imprecision		in the control groups was 1.4	in the intervention groups was 0.10 lower (1.63 lower to 1.43 higher)
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, <3 months) in the control groups was 5.8	The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, <3 months) in the intervention groups was 0.60 higher (0.90 lower to 2.10 higher)
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, >3 months) in the control groups was 5.8	The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, >3 months) in the intervention groups was 0.10 higher (1.18 lower to 1.38 higher)
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, <3 months) in the control groups was 14.3	The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 1.60 higher (0.91 lower to 4.11 higher)
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, >3 months) in the control groups was 13.9	The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 1.80 lower (4.42 lower to 0.82 higher)
ADHD symptoms (inattention, parent, SWAN, 0-3, high is poor, FV, PT <3 months)	75 (1 study) 10-12 weeks	LOW[b,d] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, swan, high is poor, fv, pt <3 months) in the control groups was 1.11	The mean ADHD symptoms (inattention, parent, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.50 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants (95% CI)
					(0.84 to 0.16 lower)
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 10.2	The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 2.30 higher (0.55 lower to 5.15 higher)
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 14.8	The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 1.70 lower (4.53 lower to 1.13 higher)
ADHD symptoms (inattention, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)	72 (1 study) 10-12 weeks	LOW[b,d] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, swan, high is poor, fv, pt <3 months) in the control groups was 1.3	The mean ADHD symptoms (inattention, teacher, swan, high is poor, fv, pt <3 months) in the intervention groups was 0.73 lower (1.09 to 0.37 lower)
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, <3 months) in the control groups was 6.5	The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, <3 months) in the intervention groups was 0.20 higher (1.02 lower to 1.42 higher)
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, FU, >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, >3 months) in the control groups was 5.6	The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, >3 months) in the intervention groups was 0.40 higher (0.68 lower to 1.48 higher)
ADHD symptoms (inattention,	52	VERY LOW[a,b]		The mean ADHD symptoms	The mean ADHD symptoms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants (95% CI)
self, SRQ, 1-10, high is good, CS, PT <3 months)	(1 study) <3 months	due to risk of bias, imprecision		(inattention, self, srq, 1-10, high is good, cs, pt <3 months) in the control groups was 1.8	(inattention, self, srq, 1-10, high is good, cs, pt <3 months) in the intervention groups was 0.40 lower (1.75 lower to 0.95 higher)
Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months)	51 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, cs, pt <3 months) in the control groups was 1.5	The mean academic (general, self, 1-10, high is good, cs, pt <3 months) in the intervention groups was 1.40 lower (3.22 lower to 0.42 higher)
Academic (general, self, SRQ, 1-10, high is good, PT <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, pt <3 months) in the control groups was 5.8	The mean academic (general, self, 1-10, high is good, pt <3 months) in the intervention groups was 0.60 higher (0.90 lower to 2.10 higher)
Academic (general, self, SRQ, 1-10, high is good, FU >3 months)	52 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, pt >3 months) in the control groups was 5.8	The mean academic (general, self, 1-10, high is good, pt >3 months) in the intervention groups was 0.10 higher (1.18 lower to 1.38 higher)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.
(c) Downgraded by 2 increments if the confidence interval crossed both MIDs.
(d) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

Table 7: Clinical evidence summary: Stimulants + non-specific supportive therapy versus stimulants

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + NSST (95% CI)
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, PT >3 months)	39 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, pt >3 months) in the control groups was 1.1	The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, pt >3 months) in the intervention groups was 0.10 lower (0.38 lower to 0.18 higher)
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months)	69 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, fu >3 months) in the control groups was 1	The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, fu >3 months) in the intervention groups was 0.20 lower (0.44 lower to 0.04 higher)
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months)	69 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, pt >3 months) in the control groups was 1.2	The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, pt >3 months) in the intervention groups was 0.30 lower (0.68 lower to 0.08 higher)
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months)	69 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, fu >3 months) in the control groups was 1.1	The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, fu >3 months) in the intervention groups was 0.40 lower (0.7 to 0.1 lower)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.

Table 8: Clinical evidence summary: Mixed medication versus parent/family training

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parent/family training	Risk difference with Mixed medication (95% CI)
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)	242 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean ADHD symptoms (total, teacher and parent, snap, 0-3, high is poor, fv, fu >3 months) in the control groups was 1.27	The mean ADHD symptoms (total, teacher and parent, snap, 0-3, high is poor, fv, fu >3 months) in the intervention groups was 0.06 lower (0.21 lower to 0.09 higher)
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months)	239 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, high is poor, fv, pt, >3 months) in the control groups was 1.1	The mean ADHD symptoms (hyperactivity, teacher, snap,0-3, high is poor, fv, pt, >3 months) in the intervention groups was 0.28 lower (0.47 to 0.09 lower)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	250 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, high is poor, fv, pt >3 months) in the control groups was 1.24	The mean ADHD symptoms (hyperactivity, parent, snap, 0-3,high is poor, fv, pt >3 months) in the intervention groups was 0.33 lower (0.5 to 0.16 lower)
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)	217 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, snap, 0-3, high is poor, fv, pt >3 months) in the control groups was 0.29	The mean ADHD symptoms (hyperactivity, observer, snap, 0-3,high is poor, fv, pt >3 months) in the intervention groups was 0.13 lower (0.19 to 0.07 lower)
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	250 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, snap, 0-3, high is poor, fv, pt >3 months) in the control groups was	The mean ADHD symptoms (inattention, parent, snap, 0-3, high is poor, fv, pt >3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parent/family training	Risk difference with Mixed medication (95% CI)
				1.4	0.28 lower (0.45 to 0.11 lower)
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)	240 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, snap, 0-3, high is poor, fv, pt >3 months) in the control groups was 1.47	The mean ADHD symptoms (inattention, teacher, snap, 0-3, high is poor, fv, pt >3 months) in the intervention groups was 0.36 lower (0.56 to 0.16 lower)
Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)	78 (1 study) 8 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean academic outcomes (maths accuracy %, observer, high is better, pt <3 months) in the control groups was 91.9	The mean academic outcomes (maths accuracy %, observer, high is better, pt <3 months) in the intervention groups was 4.14 lower (7.04 to 1.24 lower)
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	258 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was 100.3	The mean academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the intervention groups was 0.60 lower (3.86 lower to 2.66 higher)
Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)	75 (1 study) 8 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean academic outcomes (reading accuracy %, observer, high is better, pt <3 months) in the control groups was 91.59	The mean academic outcomes (reading accuracy %, observer ,high is better, pt <3 months) in the intervention groups was 5.45 lower (9.36 to 1.54 lower)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	258 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was	The mean academic outcomes (reading accuracy, observer , WIAT, 0-132, high is better, pt >3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parent/family training	Risk difference with Mixed medication (95% CI)
				96.2	1.70 higher (1.84 lower to 5.24 higher)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)	242 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, fu >3 months) in the control groups was 98.3	The mean academic outcomes (reading accuracy, observer , WIAT, 0-132, high is better, fu >3 months) in the intervention groups was 0.50 lower (3.98 lower to 2.98 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.
(c) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

1.5.4.1.2 Combination versus non-pharmacological treatment in children and young people

Table 9: Clinical evidence summary: Atomoxetine + parent/family training versus parent/family training

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parent/family training	Risk difference with Atomoxetine + PT/FT (95% CI)
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.45	The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.22 lower (0.54 lower to 0.1 higher)
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.46	The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.32 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parent/family training	Risk difference with Atomoxetine + PT/FT (95% CI)
					(0.72 lower to 0.08 higher)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.44	The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.29 lower (0.65 lower to 0.07 higher)
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.28	The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.30 lower (0.77 lower to 0.17 higher)
ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.45	The mean ADHD symptoms (inattention, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.15 lower (0.5 lower to 0.2 higher)
ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.64	The mean ADHD symptoms (inattention, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.34 lower (0.75 lower to 0.07 higher)
Responders by CGI-I (PT, <3 months)	62 (1 study) 10 weeks	LOW[a,b] due to risk of bias,	RR 1.67 (0.86 to 3.22)	290 per 1000	194 more per 1000 (from 41 fewer to 644 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with parent/family training	Risk difference with Atomoxetine + PT/FT (95% CI)
		imprecision			

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
2 Downgraded by 1 increment if the confidence interval crossed one MID.

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.

Table 10: Clinical evidence summary: Atomoxetine + PE versus PE

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PE	Risk difference with Atomoxetine + PE (95% CI)
Quality of life (parent rated, total CHIP-CE, unclear range, high is good outcome, CS, PT <3 months)	99 (1 study) 10 weeks	MODERATE[a] due to imprecision		The mean quality of life (parent rated, total chip-ce, unclear range, high is good outcome, cs, pt <3 months) in the control groups was 5.2	The mean quality of life (parent rated, total chip-ce, unclear range, high is good outcome, cs, pt <3 months) in the intervention groups was 1.40 higher (1.93 lower to 4.73 higher)
ADHD symptoms (total, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months)	99 (1 study) 10 weeks	HIGH		The mean ADHD symptoms (total, parent, ADHD-rs, high is poor, cs, pt, <3 months) in the control groups was -6.3	The mean ADHD symptoms (total, parent, ADHD-rs, high is poor, cs, pt, <3 months) in the intervention groups was 12.70 lower (16.86 to 8.54 lower)
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months)	99 (1 study) 10 weeks	HIGH		The mean ADHD symptoms (hyperactivity, parent, ADHD-rs, high is poor, cs, pt, <3 months) in the control groups was -2.5	The mean ADHD symptoms (hyperactivity, parent, ADHD-rs, high is poor, cs, pt, <3 months) in the intervention groups was 6.20 lower (8.42 to 3.98 lower)
ADHD symptoms (inattention,	99	HIGH		The mean ADHD symptoms	The mean ADHD symptoms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PE	Risk difference with Atomoxetine + PE (95% CI)
parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months)	(1 study) 10 weeks			(inattention, parent, ADHD-rs, high is poor, cs, pt, <3 months) in the control groups was -3.8	(inattention, parent, ADHD-rs, high is poor, cs, pt, <3 months) in the intervention groups was 6.50 lower (8.5 to 4.5 lower)
Academic (parent rated, academic CHIP-CE, unclear range, high is good outcome, CS, PT <3 months)	99 (1 study) 10 weeks	MODERATE[a] due to imprecision		The mean academic (parent rated, academic chip-ce, unclear range, high is good outcome, cs, pt <3 months) in the control groups was 2.4	The mean academic (parent rated, academic chip-ce, unclear range, high is good outcome, cs, pt <3 months) in the intervention groups was 4.30 higher (0.83 to 7.77 higher)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID.

Table 11: Clinical evidence summary: Atomoxetine + CBT versus CBT

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with Atomoxetine + CBT (95% CI)
ADHD symptoms (total, parent, DSM-IV checklist, 0-54, high is poor, CS, PT <3 months)	65 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, dsm-iv checklist, 0-54, high is poor, cs, pt <3 months) in the control groups was 8.82	The mean ADHD symptoms (total, parent, dsm-iv checklist, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 5.00 higher (1.87 lower to 11.87 higher)
ADHD symptoms (total, self, DSM-IV checklist, 0-54, high is poor, CS, PT <3 months)	65 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, dsm-iv checklist, 0-54, high is poor, cs, pt <3 months) in the control groups was 19.02	The mean ADHD symptoms (total, self, dsm-iv checklist, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.83 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with Atomoxetine + CBT (95% CI)
					(7.52 lower to 5.86 higher)
Responders by CGI-I (PT, <3 months)	65 (1 study) 12 weeks	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.88 (0.57 to 1.34)	Moderate	
				606 per 1000	73 fewer per 1000 (from 261 fewer to 206 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.
(c) Downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 12: Clinical evidence summary: Stimulants + NF versus NF

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, <3 months) in the control groups was 23.5	The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 1.10 higher (3.03 lower to 5.23 higher)
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, >3 months) in the control groups was 23.8	The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 1.10 lower (6.01 lower to 3.81 higher)
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 21	The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 0.10 higher (5.87 lower to 6.07 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 25.3	The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 3.20 lower (8.73 lower to 2.33 higher)
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, <3 months) in the control groups was 9.2	The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 0.30 higher (2.21 lower to 2.81 higher)
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, >3 months) in the control groups was 10	The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.90 higher (2.00 lower to 3.80 higher)
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 10.8	The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 2.10 lower (6.03 lower to 1.83 higher)
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,c] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 10.5	The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.00 higher (3.24 lower to 3.24 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, <3 months) in the control groups was 5.8	The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, <3 months) in the intervention groups was 1.20 higher (0.36 lower to 2.76 higher)
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, FU, >3 months)	53 (1 study) 6 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, >3 months) in the control groups was 5.8	The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, >3 months) in the intervention groups was 0.10 higher (1.18 lower to 1.38 higher)
ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months)	50 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self, srq, 1-10, high is good, cs, pt <3 months) in the control groups was 1.4	The mean ADHD symptoms (hyperactivity, self, srq, 1-10, high is good, cs, pt <3 months) in the intervention groups was 0.40 lower (2 lower to 1.2 higher)
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, <3 months) in the control groups was 14.3	The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 0.80 higher (1.71 lower to 3.31 higher)
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, >3 months) in the control groups was 13.9	The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 2.10 lower (4.79 lower to 0.59 higher)
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is	60 (1 study)	VERY LOW[a,b] due to risk of		The mean ADHD symptoms (inattention, teacher, barkley's,	The mean ADHD symptoms (inattention, teacher, barkley's,

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants + NF (95% CI)
poor, PT, <3 months)	3 months	bias, imprecision		high is poor, pt, <3 months) in the control groups was 10.2	high is poor, pt, <3 months) in the intervention groups was 2.20 higher (0.78 lower to 5.18 higher)
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 14.8	The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 3.20 lower (6.17 to 0.23 lower)
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, <3 months) in the control groups was 6.5	The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, <3 months) in the intervention groups was 0.20 lower (1.42 lower to 1.02 higher)
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, FU, >3 months)	53 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, >3 months) in the control groups was 5.6	The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, >3 months) in the intervention groups was 1.30 higher (0.22 to 2.38 higher)
ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months)	50 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self, srq, 1-10, high is good, cs, pt <3 months) in the control groups was 1.8	The mean ADHD symptoms (inattention, self, srq, 1-10, high is good, cs, pt <3 months) in the intervention groups was 0.60 lower (1.88 lower to 0.68 higher)
Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months)	46 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, cs, pt <3 months) in the control groups was	The mean academic (general, self, 1-10, high is good, cs, pt <3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NF	Risk difference with Stimulants + NF (95% CI)
				1.5	2.50 lower (4.31 to 0.69 lower)
Academic (general, self, SRQ, 1-10, high is good, PT <3 months)	60 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, pt <3 months) in the control groups was 5.8	The mean academic (general, self, 1-10, high is good, pt <3 months) in the intervention groups was 1.20 higher (0.36 lower to 2.76 higher)
Academic (general, self, SRQ, 1-10, high is good, FU >3 months)	53 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, pt >3 months) in the control groups was 5.8	The mean academic (general, self, 1-10, high is good, pt >3 months) in the intervention groups was 0.10 higher (1.18 lower to 1.38 higher)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.
(c) Downgraded by 2 increments if the confidence interval crosses 2 MIDs.

Table 13: Clinical evidence summary: Stimulants + CBT versus CBT

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with Stimulants + CBT (95% CI)
ADHD symptoms (total, observer, ADHD-RS, 0-68, high is poor, FV, PT, >3 months)	303 (1 study) 16 weeks	HIGH		The mean ADHD symptoms (total, observer, ADHD-rs, 0-68, high is poor, fv, pt, >3 months) in the control groups was 16.4	The mean ADHD symptoms (total, observer, ADHD-rs, 0-68, high is poor, fv, pt, >3 months) in the intervention groups was 0.60 higher (1.04 lower to 2.24 higher)

Table 14: Clinical evidence summary: Mixed medication + PT/FT versus PT/FT

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PT/FT	Risk difference with Mixed medication + PT/FT (95% CI)
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)	254 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean ADHD symptoms (total, teacher and parent, snap, high is poor, fv, fu >3 months) in the control groups was 1.27	The mean ADHD symptoms (total, teacher and parent, snap, high is poor, fv, fu >3 months) in the intervention groups was 0.07 lower (0.21 lower to 0.07 higher)
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months)	253 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, snap, high is poor, fv, pt, >3 months) in the control groups was 1.1	The mean ADHD symptoms (hyperactivity, teacher, snap, high is poor, fv, pt, >3 months) in the intervention groups was 0.35 lower (0.53 to 0.17 lower)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	262 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean ADHD symptoms (hyperactivity, parent, snap, high is poor, fv, pt >3 months) in the control groups was 1.24	The mean ADHD symptoms (hyperactivity, parent, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.61 higher (0.45 to 0.77 higher)
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)	221 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, snap, high is poor, fv, pt >3 months) in the control groups was 0.29	The mean ADHD symptoms (hyperactivity, observer, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.08 lower (0.14 to 0.02 lower)
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	262 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, snap, high is poor, fv, pt >3 months) in the control groups was 1.4	The mean ADHD symptoms (inattention, parent, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.38 lower (0.54 to 0.22 lower)
ADHD symptoms (inattention,	254	LOW[a,b]		The mean ADHD symptoms	The mean ADHD symptoms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PT/FT	Risk difference with Mixed medication + PT/FT (95% CI)
teacher, SNAP, 0-3, high is poor, FV, PT >3 months)	(1 study) 14 months	due to risk of bias, imprecision		(inattention, teacher, snap, high is poor, fv, pt >3 months) in the control groups was 1.47	(inattention, teacher, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.35 lower (0.54 to 0.16 lower)
Academic outcomes (maths accuracy %, high is better, observer, PT <3 months)	78 (1 study) 8 days	VERY LOW[b,c] due to risk of bias, imprecision		The mean academic outcomes (maths accuracy %, observer, high is better, pt <3 months) in the control groups was 91.89	The mean academic outcomes (maths accuracy %, observer, high is better, pt <3 months) in the intervention groups was 0.99 lower (3.42 lower to 1.44 higher)
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	270 (1 study) 8 weeks	LOW[c] due to risk of bias		The mean academic outcomes (maths accuracy, observer, WIAT, 0-132,high is better, pt >3 months) in the control groups was 100.3	The mean academic outcomes (maths accuracy, observer, WIAT, 0-132,high is better, pt >3 months) in the intervention groups was 0.20 higher (3.4 lower to 3.8 higher)
Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)	75 (1 study) 8 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean academic outcomes (reading accuracy %, observer, high is better, pt <3 months) in the control groups was 91.59	The mean academic outcomes (reading accuracy %, observer, high is better, pt <3 months) in the intervention groups was 1.17 lower (4.34 lower to 2 higher)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	270 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was 96.2	The mean academic outcomes (reading accuracy, observer, WIAT, 0-132,high is better, pt >3 months) in the intervention groups was 3.20 higher (0.39 lower to 6.79 higher)
Academic outcomes (reading	254	MODERATE[a]		The mean academic outcomes	The mean academic outcomes

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with PT/FT	Risk difference with Mixed medication + PT/FT (95% CI)
accuracy, observer, WIAT, 0-132, high is better, FU >3 months)	(1 study) 14 months	due to risk of bias		(reading accuracy, observer, WIAT, 0-132,high is better, fu >3 months) in the control groups was 98.3	(reading accuracy, observer, WIAT, 0-132,high is better, fu >3 months) in the intervention groups was 0.60 lower (4.02 lower to 2.82 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.
(c) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

15.4.1.3 Combination versus pharmacological treatment in children and young people

Table 15: Clinical evidence summary: Atomoxetine + PT/FT versus atomoxetine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Atomoxetine	Risk difference with Atomoxetine + PT/FT (95% CI)
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.24	The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.01 lower (0.32 lower to 0.3 higher)
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.49	The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.35 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Atomoxetine	Risk difference with Atomoxetine + PT/FT (95% CI)
					(0.73 lower to 0.03 higher)
ADHD symptoms (hyperactivity, parent, multiple scales, higher is worse, FV, PT <3 months)	120 (2 studies) 8-10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, multiple scales, higher is worse, fv, pt <3 months) in the control groups was 1.19	The mean ADHD symptoms (hyperactivity, parent, multiple scales, higher is worse, fv, pt <3 months) in the intervention groups was 0.21 standard deviations lower (0.57 lower to 0.15 higher)
ADHD symptoms (hyperactivity, teacher, multiple scales, higher is worse, FV, PT <3 months)	120 (2 studies) 8-10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, multiple scales, higher is worse, fv, pt <3 months) in the control groups was 1.13	The mean ADHD symptoms (hyperactivity, teacher, multiple scales, higher is worse, fv, pt <3 months) in the intervention groups was 0.16 standard deviations lower (0.52 lower to 0.2 higher)
ADHD symptoms (inattention, parent, multiple scales, higher is worse, FV, PT <3 months)	120 (2 studies) 8-10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, multiple scales, higher is worse, fv, pt <3 months) in the control groups was 1.50	The mean ADHD symptoms (inattention, parent, multiple scales, higher is worse, fv, pt <3 months) in the intervention groups was 0.37 standard deviations lower (0.73 to 0.01 lower)
ADHD symptoms (inattention, teacher, multiple scales, higher is worse, FV, PT <3 months)	120 (2 studies) 8-10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, multiple scales, higher is worse, fv, pt <3 months) in the control groups was 1.52	The mean ADHD symptoms (inattention, teacher, multiple scales, higher is worse, fv, pt <3 months) in the intervention groups was 0.38 standard deviations lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Atomoxetine	Risk difference with Atomoxetine + PT/FT (95% CI)
					(0.74 to 0.02 lower)
Responders by CGI-I (PT, <3 months)	119 (2 studies) 8-10 weeks	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.05 (0.73 to 1.5)	Moderate	
				494 per 1000	25 more per 1000 (from 133 fewer to 247 more)
Behaviour/function (behaviour, 0-100, high is good, teacher, PT, <3 months)	56 (1 study) 8 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (behaviour, 0-100, high is good, teacher, pt, <3 months) in the control groups was 77.84	The mean behaviour/function (behaviour, 0-100, high is good, teacher, pt, <3 months) in the intervention groups was 5.06 higher (4.59 lower to 14.71 higher)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.
(c) Downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 16: Clinical evidence summary: Stimulants + PT/FT versus stimulants

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + PT/FT (95% CI)
ADHD symptoms (total, parent, multiple scales, high is poor, FV, PT, >3 months)	224 (3 studies) 2-12 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, multiple scales, high is poor, fv, pt, >3 months) in the control groups was 4.44	The mean ADHD symptoms (total, parent, multiple scales, high is poor, fv, pt, >3 months) in the intervention groups was 0.42 standard deviations lower (0.69 to 0.15 lower)
ADHD symptoms (total, parent, SWAN, 0-3, high is poor, FV, FU, >3 months)	75 (1 study) 12 months	LOW[a,b] due to risk of bias,		The mean ADHD symptoms (total, parent, swan, 0-3, high is poor, fv, fu, >3 months) in	The mean ADHD symptoms (total, parent, swan, 0-3, high is poor, fv, fu, >3 months) in

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + PT/FT (95% CI)
		imprecision		the control groups was 0.71	the intervention groups was 0.13 lower (0.39 lower to 0.13 higher)
ADHD symptoms (total, teacher, DBDRS, 0-54, high is poor, FV, PT, <3 months)	45 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, dbdrs, 0-54, high is poor, fv, pt, <3 months) in the control groups was 13.75	The mean ADHD symptoms (total, teacher, dbdrs, 0-54, high is poor, fv, pt, <3 months) in the intervention groups was 2.15 higher (3.48 lower to 7.78 higher)
ADHD symptoms (hyperactivity, parent, FBB-ADHS, 0-3, high is poor, FV, PT, >3 months)	137 (2 studies) 12 months	MODERATE[a] due to risk of bias		The mean ADHD symptoms (hyperactivity, parent, fbb-adhs, 0-3, high is poor, fv, pt, >3 months) in the control groups was 1.26	The mean ADHD symptoms (hyperactivity, parent, fbb-adhs, 0-3, high is poor, fv, pt, >3 months) in the intervention groups was 0.05 standard deviations lower (0.35 lower to 0.25 higher)
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months)	68 (1 study) 12 months	VERY LOW[b,c] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, fu >3 months) in the control groups was 1	The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, fu >3 months) in the intervention groups was 0.10 lower (0.36 lower to 0.16 higher)
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months)	68 (1 study) 12 months	VERY LOW[b,c] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, pt >3 months) in the control groups was 1.2	The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, pt >3 months) in the intervention groups was 0.30 lower (0.7 lower to 0.1 higher)
ADHD symptoms (hyperactivity,	68	VERY LOW[b,c]		The mean ADHD symptoms	The mean ADHD symptoms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + PT/FT (95% CI)
teacher, CTRS, 0-3, higher is worse, FV, FU >3 months)	(1 study) 12 months	due to risk of bias, imprecision		(hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, fu >3 months) in the control groups was 1.1	(hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, fu >3 months) in the intervention groups was 0.10 lower (0.46 lower to 0.26 higher)
ADHD symptoms (inattention, parent, FBB-ADHS, 0-3, high is poor, FV, PT, >3 months)	103 (1 study) 12 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, fbb-adhs, 0-3, high is poor, fv, pt, >3 months) in the control groups was 1.67	The mean ADHD symptoms (inattention, parent, fbb-adhs, 0-3, high is poor, fv, pt, >3 months) in the intervention groups was 0.29 lower (0.53 to 0.05 lower)
Behaviour/function (function, parent, WFIRS-P, 0-3, high is poor, FV, PT, >3 months)	103 (1 study) 12 months	LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (function, parent, wfirs-p, 0-3, high is poor, fv, pt, >3 months) in the control groups was 0.96	The mean behaviour/function (function, parent, wfirs-p, 0-3, high is poor, fv, pt, >3 months) in the intervention groups was 0.10 lower (0.3 lower to 0.1 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.
(c) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 17: Clinical evidence summary: Stimulants + PT/FT versus stimulants + NSST

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with stimulants + NSST	Risk difference with Stimulants + PT/FT versus stimulants + NSST (95% CI)
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, PT >3 months)	69 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, pt >3 months) in the control groups	The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, pt >3 months) in the intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with stimulants + NSST	Risk difference with Stimulants + PT/FT versus stimulants + NSST (95% CI)
				was 1	groups was 0.20 higher (0.08 lower to 0.48 higher)
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months)	69 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, fu >3 months) in the control groups was 0.8	The mean ADHD symptoms (hyperactivity, parent, ctrs, 0-3, higher is worse, fv, fu >3 months) in the intervention groups was 0.10 higher (0.11 lower to 0.31 higher)
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months)	69 (1 study) 12 months	LOW[a] due to risk of bias		The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, pt >3 months) in the control groups was 0.9	The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, pt >3 months) in the intervention groups was 0 higher (0.36 lower to 0.36 higher)
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months)	69 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, fu >3 months) in the control groups was 0.7	The mean ADHD symptoms (hyperactivity, teacher, ctrs, 0-3, higher is worse, fv, fu >3 months) in the intervention groups was 0.30 higher (0.03 to 0.57 higher)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.

Table 18: Clinical evidence summary: Stimulants + attention/memory/cognitive training compared to stimulants

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Stimulants	Risk difference with Stimulants + attention/memory/cognitive training (95% CI)
ADHD symptoms (total, parent, Conners 48, 0-70, high is poor, FV, <3 months PT)	48 (1 study) <3 months	LOW[a] due to risk of bias		The mean ADHD symptoms (total, parent, conners 48, high is poor, fv, <3 months pt) in the control groups was 58.4	The mean ADHD symptoms (total, parent, conners 48, high is poor, fv, <3 months pt) in the intervention groups was 8.67 lower (11.5 to 5.84 lower)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 19: Clinical evidence summary: Stimulants + NF versus stimulants

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, <3 months) in the control groups was 28.1	The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 3.50 lower (7.57 lower to 0.57 higher)
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, FU, >3 months)	0 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, >3 months) in the control groups was 23.5	The mean ADHD symptoms (total, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.80 lower (5.67 lower to 4.07 higher)
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 23.7	The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 2.60 lower (8.51 lower to 3.31 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 26.1	The mean ADHD symptoms (total, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 4.00 lower (9.55 lower to 1.55 higher)
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, <3 months) in the control groups was 12.2	The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 2.70 lower (5.14 to 0.26 lower)
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, >3 months) in the control groups was 11.4	The mean ADHD symptoms (hyperactivity, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.50 lower (3.27 lower to 2.27 higher)
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, <3 months) in the control groups was 11.2	The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, <3 months) in the intervention groups was 2.50 lower (6.37 lower to 1.37 higher)
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 13.1	The mean ADHD symptoms (hyperactivity, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 1.50 lower (5.64 lower to 2.64 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, <3 months) in the control groups was 6.4	The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, <3 months) in the intervention groups was 0.60 higher (0.83 lower to 2.03 higher)
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,c] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, >3 months) in the control groups was 5.9	The mean ADHD symptoms (hyperactivity, self-rated, srq, 1-10, high is poor, pt, >3 months) in the intervention groups was 0.00 higher (1.22 lower to 1.22 higher)
ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months)	52 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self, srq, 1-10, high is good, cs, pt <3 months) in the control groups was 1.3	The mean ADHD symptoms (hyperactivity, self, srq, 1-10, high is good, cs, pt <3 months) in the intervention groups was 0.30 lower (1.87 lower to 1.27 higher)
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, <3 months) in the control groups was 15.9	The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, <3 months) in the intervention groups was 0.80 lower (3.05 lower to 1.45 higher)
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, >3 months) in the control groups was 12.1	The mean ADHD symptoms (inattention, parent, barkley's, high is poor, pt, >3 months) in the intervention groups was 0.30 lower (2.94 lower to 0 higher)
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high	61 (1 study)	VERY LOW[a,b] due to risk of		The mean ADHD symptoms (inattention, teacher, barkley's,	The mean ADHD symptoms (inattention, teacher, barkley's,

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + NF (95% CI)
is poor, PT, <3 months)	3 months	bias, imprecision		high is poor, pt, <3 months) in the control groups was 12.5	high is poor, pt, <3 months) in the intervention groups was 0.10 lower (3.16 lower to 2.96 higher)
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, >3 months) in the control groups was 13.1	The mean ADHD symptoms (inattention, teacher, barkley's, high is poor, pt, >3 months) in the intervention groups was 1.50 lower (4.48 lower to 1.48 higher)
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, <3 months) in the control groups was 6.7	The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, <3 months) in the intervention groups was 0.40 lower (1.62 lower to 0.82 higher)
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, FU, >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, >3 months) in the control groups was 6	The mean ADHD symptoms (inattention, self-rated, srq, 1-10, high is poor, pt, >3 months) in the intervention groups was 0.90 higher (0.18 lower to 1.98 higher)
ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months)	52 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self, srq, 1-10, high is good, cs, pt <3 months) in the control groups was 1.4	The mean ADHD symptoms (inattention, self, srq, 1-10, high is good, cs, pt <3 months) in the intervention groups was 0.20 lower (1.58 lower to 1.18 higher)
Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months)	49 (1 study) <3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, cs, pt <3 months) in the control groups was	The mean academic (general, self, 1-10, high is good, cs, pt <3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants	Risk difference with Stimulants + NF (95% CI)
				0.1	1.10 lower (2.84 lower to 0.64 higher)
Academic (general, self, SRQ, 1-10, high is good, PT <3 months)	61 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, pt <3 months) in the control groups was 6.4	The mean academic (general, self, 1-10, high is good, pt <3 months) in the intervention groups was 0.60 higher (0.83 lower to 2.03 higher)
Academic (general, self, SRQ, 1-10, high is good, FU >3 months)	57 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean academic (general, self, 1-10, high is good, pt >3 months) in the control groups was 5.9	The mean academic (general, self, 1-10, high is good, pt >3 months) in the intervention groups was 0.00 higher (1.22 lower to 1.22 higher)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.
(c) Downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 20: Clinical evidence summary: Mixed medication + PT/FT versus mixed medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + PT/FT (95% CI)
ADHD symptoms (total, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months)	270 (1 study) 12 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (total, parent, 0-54, high is poor, cs, fu, >3 months) in the intervention groups was 0.27 standard deviations lower (0.51 to 0.03 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + PT/FT (95% CI)
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)	242 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean ADHD symptoms (total, teacher and parent, snap, high is poor, fv, fu >3 months) in the control groups was 1.21	The mean ADHD symptoms (total, teacher and parent, snap, high is poor, fv, fu >3 months) in the intervention groups was 0.01 lower (0.15 lower to 0.13 higher)
ADHD symptoms (hyperactivity, teacher, Conner's, 0-20, high is poor, FV, PT, <3 months)	54 (1 study) 3 months	VERY LOW[c,d] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, conner's, high is poor, fv, pt, <3 months) in the control groups was 13.93	The mean ADHD symptoms (hyperactivity, teacher, conner's, high is poor, fv, pt, <3 months) in the intervention groups was 2.22 higher (4.38 lower to 8.82 higher)
ADHD symptoms (hyperactivity, teacher, multiple scales, high is poor, FV, PT, >3 months)	309 (2 studies) 3-14 months	MODERATE[b] due to risk of bias		The mean ADHD symptoms (hyperactivity, teacher, multiple scales, high is poor, fv, pt, >3 months) in the control groups was 3.13	The mean ADHD symptoms (hyperactivity, teacher, multiple scales, high is poor, fv, pt, >3 months) in the intervention groups was 0.05 standard deviations lower (0.28 lower to 0.17 higher)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	254 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean ADHD symptoms (hyperactivity, parent, snap, high is poor, fv, pt >3 months) in the control groups was 0.91	The mean ADHD symptoms (hyperactivity, parent, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.94 higher (0.78 to 1.1 higher)
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)	224 (1 study) 14 months	LOW[b,c] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, snap, high is poor, fv, pt >3 months) in the control groups	The mean ADHD symptoms (hyperactivity, observer, snap, high is poor, fv, pt >3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + PT/FT (95% CI)
				was 0.16	0.05 higher (0 to 0.1 higher)
ADHD symptoms (hyperactivity, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months)	270 (1 study) 12 months	LOW[d] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (hyperactivity, parent, 0-54, high is poor, cs, fu, >3 months) in the intervention groups was 0.22 standard deviations lower (0.46 lower to 0.02 higher)
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	254 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean ADHD symptoms (inattention, parent, snap, high is poor, fv, pt >3 months) in the control groups was 1.12	The mean ADHD symptoms (inattention, parent, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.10 lower (0.27 lower to 0.07 higher)
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)	254 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean ADHD symptoms (inattention, teacher, snap, high is poor, fv, pt >3 months) in the control groups was 1.11	The mean ADHD symptoms (inattention, teacher, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.01 higher (0.18 lower to 0.2 higher)
ADHD symptoms (inattention, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months)	270 (1 study) 12 months	VERY LOW[c,d] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (inattention, parent, 0-54, high is poor, cs, fu, >3 months) in the intervention groups was 0.27 standard deviations lower (0.51 to 0.03 lower)
Behaviour/function (CBRS aggressive behaviour subscale, 0-15, high is poor, teacher, PT <3 months)	53 (1 study) 3 months	VERY LOW[c,d] due to risk of bias,		The mean behaviour/function (cbrs aggressive behaviour subscale, high is poor,	The mean behaviour/function (cbrs aggressive behaviour subscale, high is poor,

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + PT/FT (95% CI)
		imprecision		teacher, pt <3 months) in the control groups was 11.58	teacher, pt <3 months) in the intervention groups was 1.58 lower (8.11 lower to 4.95 higher)
Behaviour/function (CBRS aggressive behaviour subscale, 0-15, high is poor, teacher, PT >3 months)	55 (1 study) 6 months	VERY LOW[c,d] due to risk of bias, imprecision		The mean behaviour/function (cbrs aggressive behaviour subscale, high is poor, teacher, pt >3 months) in the control groups was 12.78	The mean behaviour/function (cbrs aggressive behaviour subscale, high is poor, teacher, pt >3 months) in the intervention groups was 2.28 lower (8.8 lower to 4.24 higher)
Emotional dysregulation (CBRS emotional distress subscale, 0-20, high is poor, teacher, PT <3 months)	53 (1 study) 3 months	VERY LOW[c,d] due to risk of bias, imprecision		The mean emotional dysregulation (cbrs emotional distress subscale, high is poor, teacher, pt <3 months) in the control groups was 13.04	The mean emotional dysregulation (cbrs emotional distress subscale, high is poor, teacher, pt <3 months) in the intervention groups was 4.22 higher (2.14 lower to 10.58 higher)
Emotional dysregulation (CBRS emotional distress subscale, 0-20, high is poor, teacher, PT >3 months)	55 (1 study) 6 months	VERY LOW[c,d] due to risk of bias, imprecision		The mean emotional dysregulation (cbrs emotional distress subscale, high is poor, teacher, pt >3 months) in the control groups was 14.44	The mean emotional dysregulation (cbrs emotional distress subscale, high is poor, teacher, pt >3 months) in the intervention groups was 2.35 higher (4.16 lower to 8.86 higher)
Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)	75 (1 study) 8 weeks	VERY LOW[c,d] due to risk of bias, imprecision		The mean academic outcomes (maths accuracy %, observer, high is better, pt <3 months) in the control groups was 87.75	The mean academic outcomes (maths accuracy %, observer, high is better, pt <3 months) in the intervention groups was 3.15 higher (0.15 to 6.15 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + PT/FT (95% CI)
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	260 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was 99.7	The mean academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the intervention groups was 0.80 higher (2.78 lower to 4.38 higher)
Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)	75 (1 study) 8 weeks	VERY LOW[c,d] due to risk of bias, imprecision		The mean academic outcomes (reading accuracy %, observer, high is better, pt <3 months) in the control groups was 86.14	The mean academic outcomes (reading accuracy %, observer, high is better, pt <3 months) in the intervention groups was 4.28 higher (0.3 to 8.26 higher)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	260 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was 97.9	The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the intervention groups was 1.50 higher (2.06 lower to 5.06 higher)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)	242 (1 study) 14 months	MODERATE[b] due to risk of bias		The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, fu >3 months) in the control groups was 97.8	The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, fu >3 months) in the intervention groups was 0.10 lower (3.53 lower to 3.33 higher)
Academic outcomes (general, CBRS academic subscale, 0-30, high is poor, teacher, PT <3 months)	50 (1 study) 3 months	VERY LOW[c,d] due to risk of bias, imprecision		The mean academic outcomes (general, cbrs academic subscale, high is poor, teacher, pt <3 months)	The mean academic outcomes (general, cbrs academic subscale, high is poor, teacher, pt <3 months)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + PT/FT (95% CI)
				in the control groups was 17.88	in the intervention groups was 2.25 higher (4.95 lower to 9.45 higher)
Academic outcomes (general, CBRS academic subscale, 0-30, high is poor, teacher, PT >3 months)	53 (1 study) 6 months	VERY LOW[c,d] due to risk of bias, imprecision		The mean academic outcomes (general, cbrs academic subscale, high is poor, teacher, pt >3 months) in the control groups was 21.52	The mean academic outcomes (general, cbrs academic subscale, high is poor, teacher, pt >3 months) in the intervention groups was 0.48 lower (7.09 lower to 6.13 higher)

(a) Control group not available.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(c) Downgraded by 1 increment if the confidence interval crossed 1MID.
(d) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 21: Clinical evidence summary: Mixed medication + CBT versus mixed medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + CBT (95% CI)
ADHD symptoms (total, self, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	92 (1 study) 4 months	MODERATE[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (total, self, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 1.08 standard deviations lower (1.52 to 0.64 lower)
ADHD symptoms (total, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months)	119 (1 study) 12 sessions	LOW[c] due to risk of bias		The mean ADHD symptoms (total, self, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the control groups was	The mean ADHD symptoms (total, self, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + CBT (95% CI)
				26.09	7.62 lower (7.98 to 7.26 lower)
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months)	119 (1 study) 12 sessions	LOW[c] due to risk of bias		The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the control groups was 28.44	The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the intervention groups was 9.39 lower (9.79 to 8.99 lower)
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	92 (1 study) 4 months	MODERATE[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 2.21 standard deviations lower (2.74 to 1.69 lower)
ADHD symptoms (hyperactivity, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months)	119 (1 study) 12 sessions	LOW[c] due to risk of bias		The mean ADHD symptoms (hyperactivity, self, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the control groups was 11.72	The mean ADHD symptoms (hyperactivity, self, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the intervention groups was 3.43 lower (3.74 to 3.12 lower)
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months)	119 (1 study) 12 sessions	LOW[c] due to risk of bias		The mean ADHD symptoms (hyperactivity, parent, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the control groups was 11.56	The mean ADHD symptoms (hyperactivity, parent, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the intervention groups was 3.84 lower (4.12 to 3.56 lower)
ADHD symptoms (inattention, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months)	119 (1 study) 12 sessions	LOW[c] due to risk of bias		The mean ADHD symptoms (inattention, self, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the control groups	The mean ADHD symptoms (inattention, self, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + CBT (95% CI)
				was 14.47	groups was 4.33 lower (4.51 to 4.15 lower)
ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months)	119 (1 study) 12 sessions	LOW[c] due to risk of bias		The mean ADHD symptoms (inattention, parent, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the control groups was 16.99	The mean ADHD symptoms (inattention, parent, ADHD-rs, 0-54, high is poor, fv, pt >3 months) in the intervention groups was 5.68 lower (5.89 to 5.47 lower)

1 Control group not available.
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
3 Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(a) Control group not available.
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(c) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 22: Clinical evidence summary: Mixed medication + PE versus mixed medication + NSST

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication + NSST	Risk difference with Mixed medication + PE (95% CI)
ADHD symptoms (hyperactivity, parent, CPRS, 0-27, high is poor, FV, PT <3 months)	78 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, cprs, 0-27, high is poor, fv, pt <3 months) in the control groups was 8.45	The mean ADHD symptoms (hyperactivity, parent, cprs, 0-27, high is poor, fv, pt <3 months) in the intervention groups was 1.71 lower (3.67 lower to 0.25 higher)
ADHD symptoms (hyperactivity,	76	LOW[a,b]		The mean ADHD symptoms	The mean ADHD symptoms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication + NSST	Risk difference with Mixed medication + PE (95% CI)
parent, CPRS, 0-27, high is poor, FV, FU >3 months)	(1 study) 64 weeks	due to risk of bias, imprecision		(hyperactivity, parent, cprs, 0-27, high is poor, fv, fu >3 months) in the control groups was 8.47	(hyperactivity, parent, cprs, 0-27, high is poor, fv, fu >3 months) in the intervention groups was 1.07 lower (3.02 lower to 0.88 higher)
ADHD symptoms (inattention, parent, CPRS, 0-27, high is poor, FV, PT <3 months)	78 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, cprs, 0-27, high is poor, fv, pt <3 months) in the control groups was 11	The mean ADHD symptoms (inattention, parent, cprs, 0-27, high is poor, fv, pt <3 months) in the intervention groups was 3.05 lower (4.63 to 1.47 lower)
ADHD symptoms (inattention, parent, CPRS, 0-27, high is poor, FV, FU >3 months)	76 (1 study) 64 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, cprs, 0-27, high is poor, fv, fu >3 months) in the control groups was 10.41	The mean ADHD symptoms (inattention, parent, cprs, 0-27, high is poor, fv, fu >3 months) in the intervention groups was 2.15 lower (3.93 to 0.37 lower)
Behaviour/function (opposition, parent, CPRS, 0-27, high is poor, FV, PT <3 months)	78 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (opposition, parent, cprs, 0-27, high is poor, fv, pt <3 months) in the control groups was 6.18	The mean behaviour/function (opposition, parent, cprs, 0-27, high is poor, fv, pt <3 months) in the intervention groups was 1.23 lower (2.94 lower to 0.48 higher)
Behaviour/function (opposition, parent, CPRS, 0-27, high is poor, FV, FU >3 months)	76 (1 study) 64 weeks	LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (opposition, parent, cprs, 0-27, high is poor, fv, fu >3 months) in the control groups was 5.63	The mean behaviour/function (opposition, parent, cprs, 0-27, high is poor, fv, fu >3 months) in the intervention groups was 0.43 lower (2.21 lower to 1.35 higher)
Emotional dysregulation (SDQ, parent, 0-25, high is poor, FV, PT <3	76 (1 study)	MODERATE[a] due to risk of		The mean emotional dysregulation (sdq, parent, 0-	The mean emotional dysregulation (sdq, parent, 0-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication + NSST	Risk difference with Mixed medication + PE (95% CI)
months)	12 weeks	bias		25, high is poor, fv, pt <3 months) in the control groups was 3.5	25, high is poor, fv, pt <3 months) in the intervention groups was 0.11 lower (1.21 lower to 0.99 higher)
Emotional dysregulation (SDQ, parent, 0-25, high is poor, FV, FU >3 months)	76 (1 study) 64 weeks	LOW[a,b] due to risk of bias, imprecision		The mean emotional dysregulation (sdq, parent, 0-25, high is poor, fv, fu >3 months) in the control groups was 3.75	The mean emotional dysregulation (sdq, parent, 0-25, high is poor, fv, fu >3 months) in the intervention groups was 0.29 lower (1.32 lower to 0.74 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.

Table 23: Clinical evidence summary: Mixed medication + sleep intervention versus mixed medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + sleep intervention (95% CI)
ADHD symptoms (total, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months)	244 (1 study) 3 months	LOW[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (total, teacher, ADHD-rs, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.21 standard deviations lower (0.46 lower to 0.04 higher)
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months)	244 (1 study) 3 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.39 standard deviations lower (0.64 to 0.13 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + sleep intervention (95% CI)
ADHD symptoms (total, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	244 (1 study) 6 months	LOW[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (total, teacher, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 0.18 standard deviations lower (0.43 lower to 0.07 higher)
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	244 (1 study) 6 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 0.41 standard deviations lower (0.66 to 0.15 lower)
ADHD symptoms (hyperactivity, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months)	244 (1 study) 3 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (hyperactivity, teacher, ADHD-rs, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.28 standard deviations lower (0.53 to 0.03 lower)
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months)	244 (1 study) 3 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (hyperactivity, parent, ADHD-rs, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.27 standard deviations lower (0.52 to 0.02 lower)
ADHD symptoms (hyperactivity, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	244 (1 study) 6 weeks	LOW[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (hyperactivity, teacher, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 0.18 standard deviations lower (0.44 lower to 0.07 higher)
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, CS, PT >3	244 (1 study)	VERY LOW[b,c] due to risk of		1 Control group results	The mean ADHD symptoms (hyperactivity, parent, ADHD-rs, 0-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + sleep intervention (95% CI)
months)	6 months	bias, imprecision		unavailable	54, high is poor, cs, pt >3 months) in the intervention groups was 0.29 standard deviations lower (0.54 to 0.04 lower)
ADHD symptoms (inattention, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months)	244 (1 study) 3 months	LOW[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (inattention, teacher, ADHD-rs, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.11 standard deviations lower (0.36 lower to 0.14 higher)
ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months)	244 (1 study) 3 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (inattention, parent, ADHD-rs, 0-54, high is poor, cs, pt <3 months) in the intervention groups was 0.43 standard deviations lower (0.68 to 0.18 lower)
ADHD symptoms (inattention, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	244 (1 study) 6 months	LOW[b] due to risk of bias		1 Control group results unavailable	The mean ADHD symptoms (inattention, teacher, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 0.11 standard deviations lower (0.36 lower to 0.14 higher)
ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)	244 (1 study) 6 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean ADHD symptoms (inattention, parent, ADHD-rs, 0-54, high is poor, cs, pt >3 months) in the intervention groups was 0.46 standard deviations lower (0.72 to 0.21 lower)
Behaviour/function (teacher, SDQ, 0-54, high is poor, CS, <3 months PT	244 (1 study) 3 months	LOW[b] due to risk of bias		1 Control group results unavailable	The mean behaviour/function (teacher, sdq, 0-54, high is poor, cs, <3 months pt in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + sleep intervention (95% CI)
					0.25 standard deviations lower (0.5 lower to 0 higher)
Behaviour/function (teacher, SDQ, 0-54, high is poor, CS, >3 months PT	244 (1 study) 6 months	VERY LOW[b,c] due to risk of bias, imprecision		1 Control group results unavailable	The mean behaviour/function (teacher, sdq, 0-54, high is poor, cs, >3 months pt in the intervention groups was 0.32 standard deviations lower (0.57 to 0.06 lower)

(a) No control group data available.
(b) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(c) Downgraded by 1 increment if the confidence interval crossed 1MID.

Table 24: Clinical evidence summary: Mixed medication + NF compared to mixed medication

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Mixed medication	Risk difference with Mixed medication + NF (95% CI)
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, FV, PT <3 months)	36 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, fv, pt <3 months) in the control groups was 15.22	The mean ADHD symptoms (total, parent, ADHD-rs, 0-54, high is poor, fv, pt <3 months) in the intervention groups was 4.44 lower (7.07 to 1.81 lower)
Behaviour/function (CBRS, parent, unclear scale, high is poor, FV, PT <3 months)	36 (1 study) 10 weeks	LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (cbrs, parent, unclear scale, high is poor, fv, pt <3 months) in the control groups was 11.33	The mean behaviour/function (cbrs, parent, unclear scale, high is poor, fv, pt <3 months) in the intervention groups was 3.72 lower (6.96 to 0.48 lower)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID.

1.5.4.1.4 *Combination versus no treatment/usual care in children and young people*

Table 25: Clinical evidence summary: Atomoxetine + PT/FT versus placebo/usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/usual care	Risk difference with Atomoxetine + PT/FT (95% CI)
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.74	The mean ADHD symptoms (total, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.51 lower (0.89 to 0.13 lower)
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.44	The mean ADHD symptoms (total, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.30 lower (0.71 lower to 0.11 higher)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.69	The mean ADHD symptoms (hyperactivity, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.54 lower (0.96 to 0.12 lower)
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.25	The mean ADHD symptoms (hyperactivity, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.27 lower (0.72 lower to 0.18 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/usual care	Risk difference with Atomoxetine + PT/FT (95% CI)
ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.79	The mean ADHD symptoms (inattention, parent, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.49 lower (0.87 to 0.11 lower)
ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)	64 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the control groups was 1.63	The mean ADHD symptoms (inattention, teacher, snap, 0-3, higher is worse, fv, pt <3 months) in the intervention groups was 0.33 lower (0.78 lower to 0.12 higher)
Responders by CGI-I (PT, <3 months)	62 (1 study) 10 weeks	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.5 (1.12 to 5.59)	Moderate	
				194 per 1000	291 more per 1000 (from 23 more to 890 more)
1 Downgraded by 2 increments if the majority of the evidence was at very high risk of bias. 2 Downgraded by 1 increment if the confidence interval crossed one MID.					

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.

Table 26: Clinical evidence summary: Mixed medication + PT/FT versus placebo/usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/usual care	Risk difference with Mixed medication + PT/FT (95% CI)
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)	243 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean ADHD symptoms (total, teacher and parent, snap, high is poor, fv, fu >3	The mean ADHD symptoms (total, teacher and parent, snap, high is poor, fv, fu >3 months) in

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/usual care	Risk difference with Mixed medication + PT/FT (95% CI)
				months) in the control groups was 1.26	the intervention groups was 0.06 lower (0.2 lower to 0.08 higher)
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months)	262 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, teacher, snap, high is poor, fv, pt, >3 months) in the control groups was 1.25	The mean ADHD symptoms (hyperactivity, teacher, snap, high is poor, fv, pt, >3 months) in the intervention groups was 0.50 lower (0.69 to 0.31 lower)
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	263 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, parent, snap, high is poor, fv, pt >3 months) in the control groups was 1.35	The mean ADHD symptoms (hyperactivity, parent, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.50 higher (0.34 to 0.66 higher)
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)	223 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean ADHD symptoms (hyperactivity, observer, snap, high is poor, fv, pt >3 months) in the control groups was 0.18	The mean ADHD symptoms (hyperactivity, observer, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.03 higher (0.02 lower to 0.08 higher)
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)	263 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, parent, snap, high is poor, fv, pt >3 months) in the control groups was 1.49	The mean ADHD symptoms (inattention, parent, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.47 lower (0.63 to 0.31 lower)
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)	262 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, teacher, snap, high is poor, fv, pt >3 months) in the control groups was 1.48	The mean ADHD symptoms (inattention, teacher, snap, high is poor, fv, pt >3 months) in the intervention groups was 0.36 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/usual care	Risk difference with Mixed medication + PT/FT (95% CI)
					(0.55 to 0.17 lower)
Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)	75 (1 study) 8 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean academic outcomes (maths accuracy%, observer, high is better, pt <3 months) in the control groups was 83.85	The mean academic outcomes (maths accuracy%, observer, high is better, pt <3 months) in the intervention groups was 7.05 higher (3.69 to 10.41 higher)
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	267 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was 100.4	The mean academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, pt >3 months) in the intervention groups was 0.10 higher (3.69 lower to 3.89 higher)
Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)	75 (1 study) 8 weeks	VERY LOW[b,c] due to risk of bias, imprecision		The mean academic outcomes (reading accuracy, %, observer, high is better, pt <3 months) in the control groups was 82.76	The mean academic outcomes (reading accuracy, %, observer, high is better, pt <3 months) in the intervention groups was 7.66 higher (3.35 to 11.97 higher)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)	267 (1 study) 14 months	LOW[a,b] due to risk of bias, imprecision		The mean academic outcomes (reading accuracy, , observer, WIAT, 0-132, high is better, pt >3 months) in the control groups was 95.4	The mean academic outcomes (reading accuracy, , observer, WIAT, 0-132, high is better, pt >3 months) in the intervention groups was 4.00 higher (0.47 to 7.53 higher)
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)	243 (1 study) 14 months	MODERATE[a] due to risk of bias		The mean academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, fu >3 months) in the control groups was	The mean academic outcomes (reading accuracy, , observer, WIAT, 0-132, high is better, fu >3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/usual care	Risk difference with Mixed medication + PT/FT (95% CI)
				96	1.70 higher (1.87 lower to 5.27 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1MID.
(c) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

1.5.4.1.5 *Combination versus other combined treatments in children and young people*

Table 27: Clinical evidence summary: Stimulants + NF versus stimulants + attention/memory/cognitive training

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants + attention/memory/cognitive training	Risk difference with Stimulants + NF (95% CI)
ADHD symptoms (total, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months)	64 (1 study) 8-20 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (total, parent, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the control groups was 41.2	The mean ADHD symptoms (total, parent, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the intervention groups was 2.60 lower (6.97 lower to 1.77 higher)
ADHD symptoms (total, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months)	64 (1 study) 8-20 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (total, teacher, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the control groups was 41.8	The mean ADHD symptoms (total, teacher, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the intervention groups was 3.90 lower (8.79 lower to 0.99 higher)
ADHD symptoms (total, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months)	60 (1 study) 6 months	MODERATE[a] due to imprecision		The mean ADHD symptoms (total, parent, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the control groups was 44.9	The mean ADHD symptoms (total, parent, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants + attention/memory/cognitive training	Risk difference with Stimulants + NF (95% CI)
					7.00 lower (10.85 to 3.15 lower)
ADHD symptoms (total, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months)	60 (1 study) 6 months	MODERATE[a] due to imprecision		The mean ADHD symptoms (total, teacher, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the control groups was 43.7	The mean ADHD symptoms (total, teacher, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the intervention groups was 8.70 lower (13.12 to 4.28 lower)
ADHD symptoms (hyperactivity, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months)	64 (1 study) 8-20 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (hyperactivity, parent, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the control groups was 17.3	The mean ADHD symptoms (hyperactivity, parent, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the intervention groups was 0.70 lower (3.42 lower to 2.02 higher)
ADHD symptoms (hyperactivity, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months)	64 (1 study) 8-20 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (hyperactivity, teacher, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the control groups was 18.4	The mean ADHD symptoms (hyperactivity, teacher, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the intervention groups was 1.60 lower (4.57 lower to 1.37 higher)
ADHD symptoms (hyperactivity, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months)	60 (1 study) 6 months	MODERATE[a] due to imprecision		The mean ADHD symptoms (hyperactivity, parent, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the control groups was 19.2	The mean ADHD symptoms (hyperactivity, parent, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the intervention groups was 3.20 lower (5.83 to 0.57 lower)
ADHD symptoms (hyperactivity, teacher, DSM-	60 (1 study)	MODERATE[a] due to		The mean ADHD symptoms (hyperactivity, teacher, dsm-iv, high	The mean ADHD symptoms (hyperactivity, teacher, dsm-

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants + attention/memory/cognitive training	Risk difference with Stimulants + NF (95% CI)
IV, high is poor, unclear scale, FV, FU >3 months)	6 months	imprecision		is poor, unclear scale, fv, fu >3 months) in the control groups was 19.8	iv, high is poor, unclear scale, fv, fu >3 months) in the intervention groups was 3.70 lower (6.89 to 0.51 lower)
ADHD symptoms (inattention, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months)	64 (1 study) 8-20 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (inattention, parent, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the control groups was 23.9	The mean ADHD symptoms (inattention, parent, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the intervention groups was 1.30 lower (3.83 lower to 1.23 higher)
ADHD symptoms (inattention, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months)	64 (1 study) 8-20 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (inattention, teacher, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the control groups was 23.6	The mean ADHD symptoms (inattention, teacher, dsm-iv, high is poor, unclear scale, fv, pt <3 months) in the intervention groups was 2.40 lower (5.1 lower to 0.3 higher)
ADHD symptoms (inattention, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months)	60 (1 study) 6 weeks	MODERATE[a] due to imprecision		The mean ADHD symptoms (inattention, parent, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the control groups was 25.7	The mean ADHD symptoms (inattention, parent, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the intervention groups was 4.10 lower (6.43 to 1.77 lower)
ADHD symptoms (inattention, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months)	60 (1 study) 6 months	HIGH		The mean ADHD symptoms (inattention, teacher, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the control groups was 25.4	The mean ADHD symptoms (inattention, teacher, dsm-iv, high is poor, unclear scale, fv, fu >3 months) in the intervention groups was 5.50 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants + attention/memory/cognitive training	Risk difference with Stimulants + NF (95% CI)
					(7.4 to 3.6 lower)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID.

1.5.4.2 Adults over the age of 18

1.5.4.2.1 Pharmacological treatment versus non-pharmacological treatment in adults

Table 28: Clinical evidence summary: stimulants + NSST versus CBT

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with Stimulants + NSST (95% CI)
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)	213 (1 study) 1 years	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the CBT groups was 16.9	The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the intervention groups was 1.80 lower (3.63 lower to 0.03 higher)
ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	210 (1 study) 1 years	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, observer, caars, high is worse, fv, >3 months pt) in the CBT groups was 16.4	The mean ADHD symptoms (total, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 1.80 lower (3.49 to 0.11 lower)
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	210 (1 study) 1 years	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the CBT groups was 14.9	The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 1.60 lower (3.41 lower to 0.21 higher)
ADHD symptoms (inattention,	213	MODERATE[a]		The mean ADHD symptoms	The mean ADHD symptoms

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT	Risk difference with Stimulants + NSST (95% CI)
observer, CAARS, 0-30, high is worse, FV, >3 months PT)	(1 study) 1 years	due to risk of bias		(inattention, observer, caars, high is worse, fv, >3 months pt) in the CBT groups was 15.2	(inattention, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 0.80 higher (0.95 lower to 2.55 higher)
Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT)	210 (1 study) 1 years	MODERATE[a] due to risk of bias		The mean emotional dysregulation (bdi, 0-63, high is poor, fv, >3 months pt) in the CBT groups was 9.4	The mean emotional dysregulation (bdi, 0-63, high is poor, fv, >3 months pt) in the intervention groups was 0.20 higher (1.77 lower to 2.17 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

1.5.4.2.2 *Combination versus non-pharmacological treatment in adults*

Table 29: Clinical evidence summary: stimulants + CBT/DBT versus CBT/DBT alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CBT/DBT alone	Risk difference with Stimulants + CBT/DBT (95% CI)
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)	209 (1 study) 1 years	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the control groups was 16.9	The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the intervention groups was 1.60 lower (2.50 to 0.70 lower)
ADHD symptoms (total, self, multiple tools, decreased by >30%, >3 months PT) - General population	106 (1 study) 14 weeks	LOW[b] due to imprecision	RR 0.86 (0.59 to 1.26)	Moderate 547 per 1000	77 fewer per 1000 (from 224 fewer to 142 more)

ADHD symptoms (total, self, multiple tools, decreased by >30%, >3 months PT) - Secure estate	53 (1 study) 24 weeks	LOW[a,b] due to risk of bias, imprecision	RR 2.34 (1.17 to 4.69)	Moderate 269 per 1000	360 more per 1000 (from 46 more to 993 more)
ADHD symptoms (total, observer, TAADDS, decreased by >30%, >3 months PT)	106 (1 study) 14 weeks	MODERATE[a] due to imprecision	RR 1.4 (0.81 to 2.41)	Moderate 283 per 1000	113 more per 1000 (from 54 fewer to 399 more)
ADHD symptoms (total, observer, multiple tools, high is worse, FV, >3 months PT)	257 (2 studies) 20-52 weeks	LOW[a,b] due to risk of bias, imprecision		Control group results unavailable	The mean ADHD symptoms (total, observer, multiple tools, high is worse, fv, >3 months pt) in the intervention groups was 0.43 standard deviations lower (0.67 to 0.18 lower)
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	209 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the control groups was 14.9	The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 1.90 lower (2.84 to 0.96 lower)
ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	209 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, observer, caars, high is worse, fv, >3 months pt) in the control groups was 16	The mean ADHD symptoms (inattention, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 1.00 lower (1.92 to 0.08 lower)
Emotional dysregulation (multiple tools, high is poor, FV, >3 months PT)	257 (2 studies) 20-52 weeks	MODERATE[a] due to risk of bias		Control group results unavailable	The mean emotional dysregulation (multiple tools, high is poor, fv, >3 months pt) in the intervention groups was 0.06 standard deviations lower (0.3 lower to 0.19 higher)
Responders by CGI-I (>3 months PT)	106	LOW[b]	RR 1.12	Moderate	

	(1 study) 14 weeks	due to imprecision	(0.65 to 1.96)	302 per 1000	36 more per 1000 (from 106 fewer to 290 more)
Responders by CGI-I (>3 months FU)	48 (1 study) 20 weeks	HIGH	RR 4.08 (1.58 to 10.5)	Moderate	
				160 per 1000	493 more per 1000 (from 93 more to 1000 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 30: Clinical evidence summary: stimulants + CBT/DBT + PT/FT versus NSST + PT/FT alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSST + PT/FT	Risk difference with Stimulants + CBT/DBT + PT/FT (95% CI)
ADHD symptoms (total, observer, CAARS, 0-36, high is poor, FV, >3 months PT)	143 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, observer, caars, 0-36, high is poor, fv, >3 months pt) in the control groups was 15.8	The mean ADHD symptoms (total, observer, caars, 0-36, high is poor, fv, >3 months pt) in the intervention groups was 2.70 lower (4.58 to 0.82 lower)
ADHD symptoms (hyperactivity, observer, CAARS, 0-36, high is poor, FV, >3 months PT)	143 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, caars, 0-36, high is poor, fv, >3 months pt) in the control groups was 13.7	The mean ADHD symptoms (hyperactivity, observer, caars, 0-36, high is poor, fv, >3 months pt) in the intervention groups was 3.00 lower (4.88 to 1.12 lower)
ADHD symptoms (inattention, observer, CAARS, 0-36, high is poor, FV, >3 months PT)	143 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, observer, caars, 0-36, high is poor, fv, >3 months pt) in the control groups was 15.1	The mean ADHD symptoms (inattention, observer, caars, 0-36, high is poor, fv, >3 months pt) in the intervention groups was 2.70 lower (4.79 to 0.61 lower)
Child's ADHD symptoms (total,	144	LOW[a,b]		The mean child's ADHD	The mean child's ADHD

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSST + PT/FT	Risk difference with Stimulants + CBT/DBT + PT/FT (95% CI)
parent, SDQ, 0-10, high is poor, FV, >3 months PT)	(1 study) 52 weeks	due to risk of bias, imprecision		symptoms (total, parent, sdq, 0-10, high is poor, fv, >3 months pt) in the control groups was 6.2	symptoms (total, parent, sdq, 0-10, high is poor, fv, >3 months pt) in the intervention groups was 0.50 lower (1.13 lower to 0.13 higher)
Emotional dysregulation (parent, SDQ, 0-10, high is poor, FV, >3 months PT)	144 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean emotional dysregulation (parent, sdq, 0-10, high is poor, fv, >3 months pt) in the control groups was 3.1	The mean emotional dysregulation (parent, sdq, 0-10, high is poor, fv, >3 months pt) in the intervention groups was 0.20 higher (0.43 lower to 0.83 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

15.4.2.3 *Combination versus pharmacological treatment in adults*

Table 31: Clinical evidence summary: stimulants + CBT/DBT versus stimulants + NSST alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants + NSST	Risk difference with Stimulants + CBT/DBT (95% CI)
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)	213 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the control groups was 15.1	The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the intervention groups was 0.20 higher (1.55 lower to 1.95 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Stimulants + NSST	Risk difference with Stimulants + CBT/DBT (95% CI)
ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	213 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean ADHD symptoms (total, observer, caars, high is worse, fv, >3 months pt) in the control groups was 14.6	The mean ADHD symptoms (total, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 0.30 higher (1.45 lower to 2.05 higher)
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	209 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the control groups was 13.3	The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 0.30 lower (1.98 lower to 1.38 higher)
ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	209 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean ADHD symptoms (inattention, observer, caars, high is worse, fv, >3 months pt) in the control groups was 15.2	The mean ADHD symptoms (inattention, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 0.20 lower (1.88 lower to 1.48 higher)
Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT)	213 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean emotional dysregulation (bdi, 0-63, high is poor, fv, >3 months pt) in the control groups was 9.6	The mean emotional dysregulation (bdi, 0-63, high is poor, fv, >3 months pt) in the intervention groups was 0.70 lower (2.66 lower to 1.26 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 32: Clinical evidence summary: mixed medication + CBT/DBT versus mixed medication alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mixed medication alone	Risk difference with mixed medication + CBT/DBT (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mixed medication alone	Risk difference with mixed medication + CBT/DBT (95% CI)
QoL (Flanagan, 16-112, high is good, FV, <3 months PT)	69 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean qol (flanagan, 16-112, high is good, fv, <3 months pt) in the control groups was 70.9	The mean qol (flanagan, 16-112, high is good, fv, <3 months pt) in the intervention groups was 3.60 higher (3.68 lower to 10.88 higher)
QoL (Flanagan, 16-112, high is good, FV, <3 months FU)	57 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean qol (flanagan, 16-112, high is good, fv, <3 months fu) in the control groups was 72.22	The mean qol (flanagan, 16-112, high is good, fv, <3 months fu) in the intervention groups was 7.62 higher (1.03 to 14.21 higher)
ADHD symptoms (total, observer, ADHD-RS, 0-54, higher is worse, FV, PT >3 months)	31 (1 study) 15 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, observer, ADHD-rs, 0-54, higher is worse, fv, pt >3 months) in the control groups was 20.8	The mean ADHD symptoms (total, observer, ADHD-rs, 0-54, higher is worse, fv, pt >3 months) in the intervention groups was 5.61 lower (12.11 lower to 0.89 higher)
ADHD symptoms (total, self, ADHD-RS, 0-54, higher is worse, FV, PT >3 months)	31 (1 study) 15 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, ADHD-rs, 0-54, higher is worse, fv, pt >3 months) in the control groups was 23.87	The mean ADHD symptoms (total, self, ADHD-rs, 0-54, higher is worse, fv, pt >3 months) in the intervention groups was 9.12 lower (15.69 to 2.55 lower)
ADHD symptoms (total, self, Barkley, 0-54, high is poor, FV, <3 months PT)	104 (2 studies) 8-12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, barkley, 0-54, high is poor, fv, <3 months pt) in the control groups was21.57	The mean ADHD symptoms (total, self, barkley, 0-54, high is poor, fv, <3 months pt) in the intervention groups was 5.01 lower (8.30 to 1.72 lower)
ADHD symptoms (total, self, Barkley, 0-54, high is poor, FV, <3 months FU)	89 (2 studies) 12 weeks	VERY LOW[a,b] due to risk of bias,		The mean ADHD symptoms (total, self, barkley, 0-54, high is poor, fv, <3 months fu) in the control groups was22.34	The mean ADHD symptoms (total, self, barkley, 0-54, high is poor, fv, <3 months fu) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mixed medication alone	Risk difference with mixed medication + CBT/DBT (95% CI)
		imprecision			8.23 lower (11.86 lower to 4.61 lower)
ADHD symptoms (hyperactivity, self, Barkley, 0-27, high is poor, FV, <3 months PT)	104 (2 studies) 8-12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self, barkley, 0-27, high is poor, fv, <3 months pt) in the control groups was 7.86	The mean ADHD symptoms (hyperactivity, self, barkley, 0-27, high is poor, fv, <3 months pt) in the intervention groups was 1.36 lower (3.46 lower to 0.74 higher)
ADHD symptoms (hyperactivity, self, Barkley, 0-27, high is poor, FV, <3 months FU)	89 (2 studies) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self, barkley, 0-27, high is poor, fv, <3 months fu) in the control groups was 8.16	The mean ADHD symptoms (hyperactivity, self, barkley, 0-27, high is poor, fv, <3 months fu) in the intervention groups was 2.97 lower (4.90 to 1.03 lower)
ADHD symptoms (inattention, self, Barkley, 0-27, high is poor, FV, <3 months PT)	104 (2 studies) 8-12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self, barkley, 0-27, high is poor, fv, <3 months pt) in the control groups was 13.71	The mean ADHD symptoms (inattention, self, barkley, 0-27, high is poor, fv, <3 months pt) in the intervention groups was 3.63 lower (5.55 to 1.71 lower)
ADHD symptoms (inattention, self, Barkley, 0-27, high is poor, FV, <3 months FU)	89 (2 studies) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self, barkley, 0-27, high is poor, fv, <3 months fu) in the control groups was 14.19	The mean ADHD symptoms (inattention, self, barkley, 0-27, high is poor, fv, <3 months fu) in the intervention groups was 5.26 lower (7.60 to 2.93 lower)
Responders by CGI (two point change in CGI-S, >3 months PT)	31 (1 study) 15 weeks	LOW[a,b] due to risk of bias, imprecision	RR 4.22 (1.08 to 16.45)	Moderate	
				133 per 1000	428 more per 1000 (from 11 more to 1000 more)
Emotional dysregulation (observer, HAM-D, 0-53, high is worse, FV, >3 months PT)	31 (1 study) 15 weeks	LOW[a,b] due to risk of bias, imprecision		The mean emotional dysregulation (observer, ham-d, 0-53, high is worse, fv, >3 months pt) in the control groups was	The mean emotional dysregulation (observer, ham-d, 0-53, high is worse, fv, >3 months pt) in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mixed medication alone	Risk difference with mixed medication + CBT/DBT (95% CI)
				10	5.56 lower (9.71 to 1.41 lower)
Emotional dysregulation (Self, BDI, 0-64, high is worse, FV, <3 months PT)	68 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean emotional dysregulation (bdi, 0-64, high is worse, fv, <3 months PT) in the control groups was 14	The mean emotional dysregulation (bdi, 0-64, high is worse, fv, <3 months pt) in the intervention groups was 5.62 lower (9.85 to 1.39 lower)
Emotional dysregulation (Self, BDI, 0-64, high is worse, FV, <3 months FU)	53 (1 study) 12 weeks	LOW[a] due to risk of bias		The mean emotional dysregulation (bdi, 0-64, high is worse, fv, <3 months fu) in the control groups was 13.14	The mean emotional dysregulation (bdi, 0-64, high is worse, fv, <3 months fu) in the intervention groups was 8.10 lower (11.72 to 4.43 lower)
Behaviour/function (Self rated, RATE antisocial scale, unclear range, high is worse, FV, <3 months PT)	68 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (rate antisocial scale, unclear range, high is worse, fv, <3 months pt) in the control groups was 10.29	The mean behaviour/function (rate antisocial scale, unclear range, high is worse, fv, <3 months pt) in the intervention groups was 1.05 lower (1.99 to 0.11 lower)
Behaviour/function (Self rated, RATE antisocial scale, unclear range, high is worse, FV, <3 months FU)	57 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean behaviour/function (rate antisocial scale, unclear range, high is worse, fv, <3 months fu) in the control groups was 11.19	The mean behaviour/function (rate antisocial scale, unclear range, high is worse, fv, <3 months fu) in the intervention groups was 2.43 lower (3.97 to 0.89 lower)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 33: Clinical evidence summary: mixed medication + CBT/DBT versus mixed medication + NSST

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Medication + NSST	Risk difference with Medication + CBT/DBT (95% CI)
QoL (QLESQ, unclear scale, high is better, FV, >3 months PT)	32 (1 study) 12 weeks	LOW[a,b] due to risk of bias, imprecision		The mean qol (qlesq, unclear scale, high is better, fv, >3 months pt) in the control groups was 207.4	The mean qol (qlesq, unclear scale, high is better, fv, >3 months pt) in the intervention groups was 33.10 higher (35.83 lower to 102.03 higher)
ADHD symptoms (total, self, ADHD-RS, high is worse, FV, 0-54, >3 months PT)	110 (2 studies) 12-15 weeks	VERY LOW[a,b] due to risk of bias, imprecision		Control group results unavailable	The mean ADHD symptoms (total, self, ADHD-rs, high is worse, fv, 0-54, >3 months pt) in the intervention groups was 0.33 standard deviations lower (0.7 lower to 0.05 higher)
ADHD symptoms (total, self, ADHD-RS, high is worse, FV, 0-54, >3 months FU)	70 (1 study) 52 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, ADHD-rs, high is worse, fv, 0-54, >3 months fu) in the control groups was 16.97	The mean ADHD symptoms (total, self, ADHD-rs, high is worse, fv, 0-54, >3 months fu) in the intervention groups was 3.58 lower (6.34 to 0.82 lower)
ADHD symptoms (hyperactivity, self, CAARS, high is worse, FV, 0-27, >3 months PT)	32 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, self, caars, high is worse, fv, 0-27, >3 months pt) in the control groups was 13.88	The mean ADHD symptoms (hyperactivity, self, caars, high is worse, fv, 0-27, >3 months pt) in the intervention groups was 1.72 higher (4.41 lower to 7.85 higher)
ADHD symptoms (inattention, self, CAARS, high is worse, FV, 0-27, >3 months PT)	32 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, self, caars, high is worse, fv, 0-27, >3 months pt) in the control groups was 18.58	The mean ADHD symptoms (inattention, self, caars, high is worse, fv, 0-27, >3 months pt) in the intervention groups was 1.35 higher (4.62 lower to 7.32 higher)
CGI-I responders (>3 months PT)	78 (1 study)	VERY LOW[a,b] due to risk of	RR 2.21 (1.17 to 4.16)	Moderate 243 per 1000	 294 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medication + NSST	Risk difference with Medication + CBT/DBT (95% CI)
	15 weeks	bias, imprecision			(from 41 more to 768 more)
Emotional dysregulation (Self, BDI, 0-63, high is worse, FV, >3 months PT)	32 (1 study) 12 weeks	VERY LOW[a,b] due to risk of bias, imprecision		The mean emotional dysregulation (bdi, 0-63, high is worse, fv, >3 months pt) in the control groups was 13.64	The mean emotional dysregulation (bdi, 0-63, high is worse, fv, >3 months pt) in the intervention groups was 1.24 lower (9.37 lower to 6.89 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1.5.4.2.4 *Combination versus no treatment/usual care in adults*

Table 34: Clinical evidence summary: Stimulants + CBT/DBT compared to NSST alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSST alone	Risk difference with Stimulants + CBT/DBT (95% CI)
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)	206 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the control groups was 18	The mean ADHD symptoms (total, self, caars, high is worse, fv, >3 months pt) in the intervention groups was 2.70 lower (4.45 to 0.95 lower)
ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	206 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (total, observer, caars, high is worse, fv, >3 months pt) in the control groups was 17.5	The mean ADHD symptoms (total, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 2.60 lower (4.49 to 0.71 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSST alone	Risk difference with Stimulants + CBT/DBT (95% CI)
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	206 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the control groups was 15.2	The mean ADHD symptoms (hyperactivity, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 2.20 lower (4.02 to 0.38 lower)
ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)	206 (1 study) 52 weeks	LOW[a,b] due to risk of bias, imprecision		The mean ADHD symptoms (inattention, observer, caars, high is worse, fv, >3 months pt) in the control groups was 17.5	The mean ADHD symptoms (inattention, observer, caars, high is worse, fv, >3 months pt) in the intervention groups was 2.50 lower (4.32 to 0.68 lower)
Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT)	206 (1 study) 52 weeks	MODERATE[a] due to risk of bias		The mean emotional dysregulation (bdi, 0-63, high is poor, fv, >3 months pt) in the control groups was 10.1	The mean emotional dysregulation (bdi, 0-63, high is poor, fv, >3 months pt) in the intervention groups was 1.20 lower (3.30 lower to 0.90 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(b) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

2008 guideline literature

One original model from CG72 in adults, looking at a combination of pharmacological and non-pharmacological treatments is included.

Details of the combination model in adults can be found in Table 35.

Published literature

No relevant health economic studies were identified from the update search.

See also the health economic study selection flow chart in Appendix C.

1.6.2 Excluded studies

Four studies were included in CG72 that could be included in the combination review. All were in children.[18 ,29 ,31 ,39 ,69]

All of these studies have been selectively excluded due to limited applicability and/or methodological limitations. These are listed in Appendix I, with reasons for exclusion given.

One original model from CG72 in children, looking at a combination of pharmacological and non-pharmacological treatments, has been selectively excluded because the clinical evidence feeding into this model is not included in the guideline clinical review (see Appendix I for more details), and will also be superseded by original modelling in children for this question.

See also the health economic study selection flow chart in appendix G.

1.6.3 Summary of studies included in the economic evidence review

Table 35: Health economic evidence profile: CBT added to medication versus medication alone in adults on medication but with clinically significant symptoms

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
CG72 Original analysis [45] [UK]	Directly applicable(a)	Potentially serious limitations (b)	Decision tree model with 1 year time horizon comparing adding 15 weeks of individual CBT on top of medication versus medication alone (in adults with ADHD who have been stabilised on medication and continue to show clinically significant symptoms). Clinical effectiveness from a single RCT (Safren 2005[51]). Includes only CBT costs.	£1,122	0.016	£65,279	No probabilistic analysis. Various one way sensitivity analyses and threshold analyses tested. The ICER stayed above the threshold under all scenarios but group CBT. However this varied wildly (from £13,566 to £535,556 per QALY in the various alternative hypotheses tested).

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial; CBT: Cognitive behavioural Therapy.

(a) UK NHS perspective. Directly relevant comparisons to the question.

(b) Based only on one study with 31 participants. Includes only intervention costs – no other cost savings utilities from a study comparing two doses of atomoxetine and may not reflect utilities associated with behavioural therapy. Extrapolation of effect over 1 year time horizon. Assuming tin the sensitivity analysis that group CBT is as effective as individual CBT. No probabilistic sensitivity analysis.

Table 36: Health economic evidence profile: combination of Atomoxetine + behavioural therapy versus atomoxetine versus behavioural therapy, in children

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Original NICE analysis [UK]	Directly applicable(a)	Potentially serious limitations (b)	Decision tree model with 1 year time horizon comparing; atomoxetine combined with behavioural therapy,	ATX versus BT = £732 Combinatio	ATX versus BT = 0.017 Combinatio	ATX versus BT = £44,175	Base case results were probabilistic based on 10,000 simulations.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			behavioural therapy, and atomoxetine, in children. Clinical effectiveness is from 3 studies included in the clinical review (with trial periods of around 10 weeks) that had relevant dichotomous outcomes. Includes adverse events from ATX. Cost included are the intervention costs, including staff costs for monitoring drug and staff resource use also used to represent costs associated with response/no response. Utilities associated with response/no response included and combined with costs to derive cost per QALY.	n versus ATX = £227	n versus ATX = 0.004	Combination versus ATX = £56,219 Behavioural therapy most cost effective. Net benefits: BT = £14,589 ATX = £14,197 Combination = £14,051	Various one way sensitivity analyses were tested; - assuming response from behavioural therapy diminishes after treatment ends; BT still most cost effective. - BT on an individual basis; ATX most cost effective. - Using alternative source of utility data; BT still most cost effective.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: BT: behavioural therapy; ATX: Atomoxetine

(a) UK NHS perspective. Directly relevant comparisons to the question. Uses EQ-5D.

(b) Based only on three trials, with varying intensity of particularly behavioural therapy interventions. No assumptions made about further sequences of treatments which may be underestimating QALYs/costs .Extrapolation of effect for behavioural therapy. No deterioration of the condition or impact of effect modelled over time.

Table 37: Health economic evidence profile: Methylphenidate + self-help behavioural therapy versus methylphenidate, in children on methylphenidate but with functional impairment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Original NICE analysis	Directly applicable(a)	Potentially serious limitations	Decision tree model with 1 year time horizon comparing; adding telephone assisted	£868	0.0076	£114,803	Base case results were probabilistic based on 10,000 simulations.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
[UK]		(b)	self-help behavioural therapy to MPH versus staying on MPH alone (in a population of children who are partial responders to the MPH). Clinical effectiveness is from a single study (trial length of 12 months) that had relevant dichotomous outcomes. Costs included are only the costs of the behavioural therapy. Utilities associated with response/no response included and combined with costs to derive cost per QALY.				Various threshold and sensitivity analyses (SA's) were tested; - Threshold analyses; cost of intervention would have to be below £151 to make intervention cost effective, equating to 2-3 sessions. Incremental QALY would have to be 0.0434. Time horizon Would have to be around 3 years. - Assuming effect increases linearly to 6 months as the phone calls are more intense up until that point, and stays at that level until 12 months (ICER = £76,407). - 2-way SA varying baseline response probability and intervention response RR showed that no level of combination of baseline risk and RR would make the intervention cost effective. - 2-way SA varying time horizon and utility gain showed that intervention can be cost effective if time horizon is generally over 3 years. - Using alternative sources of utility data; ICER still

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
							remained high.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RR: relative risk; BT: behavioural therapy; MPH: methylphenidate

(a) UK NHS perspective. Directly relevant comparisons to the question. Uses EQ-5D.

(b) Effect based only on one study. No assumptions made about other treatments or impact of behavioural therapy on the underlying resource use. No deterioration of the condition or impact of effect modelled over time. Effect felt to be underestimated.

Table 38: Health economic evidence profile: Medication + CBT versus medication, in adolescents on medication but with clinically significant symptoms

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Original NICE analysis [UK]	Directly applicable(a)	Potentially serious limitations (b)	Decision tree model with 1 year time horizon comparing; adding individual CBT on to medication versus staying on medication alone (in a population of adolescents partially responsive to medication). Clinical effectiveness is from a single study (trial length of 4 months) that had relevant dichotomous outcomes. Costs included are only the costs of the CBT. Utilities associated with response/no response included and combined with costs to derive cost per QALY.	£1,164	0.0188	£62,007	Base case results were probabilistic based on 10,000 simulations. Various threshold and sensitivity analyses (SA's) were tested; - Cost of intervention would have to be below £375 to make the intervention cost effective. Incremental QALY would have to be 0.0582. Time horizon would have to be 2.8 years. - Assuming the added effect of CBT diminishes after treatment ends (ICER = £105,192). - 2-way SA varying baseline response probability and intervention response RR showed that no level of combination of baseline risk and RR would make the intervention cost effective. - 2-way SA varying time horizon

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
							and utility gain showed that intervention can be cost effective with a longer time horizon of 2-4 years depending on utilty gain. - Using alternative sources of utility data; ICER still remained high.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; CBT: Cognitive behavioural Therapy; RR: relative risk

(a) UK NHS perspective. Directly relevant comparisons to the question. Used EQ-5D.

(b) Effect based only on one study. No assumptions made about other treatments or impact of behavioural therapy on the underlying resource use. No deterioration of the condition or impact of effect modelled over time. Effect felt to be underestimated.

1.6.4 Health economic model

The previous guideline model evaluating combination treatments in comparison to medication alone or behavioural therapy alone, in children, was based on two studies that directly compared the three interventions. The focus was on stimulants as the medication. The question on combination treatments was decided as the first priority for economic modelling because there is a highly relevant trade-off with regards to whether the benefit of any additional interventions are worth the additional cost. It is also considered highly important in mental health for patients to have choices about what treatments they might prefer. Therefore, updating the previous model which sought to compare different types of treatments as well as the combination of the two, would help inform; the treatment pathway to be recommended as to whether there is a hierarchy regarding pharmacological and non-pharmacological treatments, and also whether the combination is cost effective.

There are three models replacing the previous combination model in children, as the clinical data identified from the combination review that had dichotomous outcomes needed for any models was sparse and the committee felt that some interventions couldn't be combined together. An overview of the 3 models and their results are discussed below, with further detail in the write-up (Appendix 1).

1. Atomoxetine combination model

Model overview

Being evaluated in the model is the combination of Atomoxetine and (group) behavioural therapy, compared to Atomoxetine alone and behavioural therapy alone.

The model is a decision tree with a 1 year time horizon. Atomoxetine dose in the model is using a maintenance dose of 1.2mg/kg per day. Behavioural therapy consists of 10 weekly sessions of 1 hour of parent training with a clinical psychologist (in keeping with the behavioural therapy resource use in the parent training model). Combination treatment is the sum of both these interventions.

The population is children with ADHD, with an age range of 5-15 from the studies informing effect, with average ages of 8-11. They are mixed populations in the sense that some people in the trials have tried medication before, but there is no selective inclusion based only on previous non-response. Because patients begin treatment when they enter they model (as that was how the trials were set up) then in the interventions that include atomoxetine, there is a probability of withdrawal from the treatment because of intolerable side effects. At the end of duration of the trials (10 weeks), patients from all the treatments are either classified as responders or non-responders. Responders remain on the treatment (if it involves atomoxetine, because behavioural therapy is a short term treatment) and remain responding until the end of the model. Patients can also experience adverse events that are tolerable and do not cause them to withdraw from the treatment, but do lead to a decrement in quality of life. If a patient withdraws because of adverse events, or does not respond to the treatment and therefore stops the treatment, then they go on to what is referred to as 'other treatment'. There are no adverse events assumed from behavioural therapy.

No further lines of treatment were modelled because assumptions would be needed about what these would be, and there is a lack of data on probabilities that are dependent on prior treatment choices. An overarching state of 'other treatment' was used as a catch-all to represent other treatment that patients might go on to, i.e. an overall probability of response in the general ADHD child population in which some people may be on a variety of treatments and some people may not be on any active treatment. The cost of 'other treatment' is represented only in terms of resource use (the number of consultations

associated with responders and non-responders). This is because resource use in terms of staff consultations (with a psychiatrist or nurse) is already included as a key part of the cost of starting and continuing Atomoxetine, and therefore it made sense to continue including this resource use for the whole time horizon of the model so as not to bias against Atomoxetine or for not responding to be a cheaper outcome.

Data

3 studies inform the treatment effect of this model, with an average trial duration of 10 weeks. One comparing all 3 comparisons[21], one comparing the combination with atomoxetine alone[65], and one study compared the combination with behavioural therapy alone[58]. Note that where an intervention from the studies had a placebo pill in combination with a behavioural therapy; for the purposes of the model this is being treated as only behavioural therapy. The studies had some differences in terms of intensity of treatments, population medication status, and scales used to define response. But they were combined because they included atomoxetine as the drug. The probabilities of response for each intervention were derived from a network meta-analysis of the three studies undertaken by the health economist for to inform the model. Probability of discontinuation and adverse events was taken from the guideline clinical review.

Resource use such as doses of atomoxetine during titration and maintenance, and staff costs associated with monitoring treatments as well as the staff costs associated with behavioural therapy were elicited from the committee. Utilities were from the same source as the parent training model, as for all the models in the guideline. The utility gain from response is assumed to increase linearly over the trial period to reflect that the effect may not be immediate.

Results

The probabilistic base case results showed that behavioural therapy was the most cost effective because it had the highest net benefit, and also the ICERS of Atomoxetine compared to behavioural therapy (£44,175 per QALY), and combination treatment compared to Atomoxetine (£56,219 per QALY) were above the threshold of £20,000, demonstrating that the additional benefit does not justify the cost of the more expensive interventions.

Various sensitivity analyses were also explored; assuming the response from behavioural therapy decreases linearly from the end of treatment to end of the model for BT alone and combination arms. This showed behavioural therapy still had the highest net benefit, but atomoxetine had a lower ICER than in the base case. This is because reducing the effectiveness of behavioural therapy led to lower total QALYs for the other interventions. Another sensitivity analysis assumed behavioural therapy was individual rather than a group treatment; this increased the cost of the intervention to the extent that behavioural therapy was dominated by atomoxetine. Atomoxetine was now the most cost effective intervention because combination treatment had a very high ICER compared to atomoxetine (£399,620). A final sensitivity analysis also looked at using alternative sources of utility other than the EQ-5D. This showed that although the results were sensitive to changes in the QALY, behavioural therapy still had the highest net benefit.

This model aimed to compare the cost effectiveness of starting a combination of Atomoxetine and behavioural therapy, compared to starting Atomoxetine alone, or a course of behavioural therapy. Although Atomoxetine is a drug that would most likely not be at the beginning of the treatment pathway, the interventions included in the model are comparisons that were identified in the clinical review that had appropriate outcomes that could be utilised in a model. Therefore what the model is really answering is; in children who may be considering using atomoxetine, is it cost effective alone, or in combination with behavioural therapy, or is behavioural therapy alone the best choice in terms of cost effectiveness. What conclusions can be drawn from the model are highly dependent on the clinical data used, and the assumptions made about future pathways in the model and inputs such as resource use.

Limitations include; the clinical effect only being based on 3 studies. Bringing together the conclusions of dichotomous outcomes (what this model is based on) with the clinical review that used continuous outcomes is also a challenge as the two types of outcomes do not always agree. The committee opinion was that the clinical review in general is unlikely to have captured all the benefits of non-pharmacolgical treatment, because these are wider than just ADHD core symptoms. Other benefits also may not have been captured such as longer term impacts which are unknown, and the impact on other sectors. It was not possible to model all treatments individually and in sequences compared to each other and so assumptions (or the lack of) made about further treatment is also a limitation.

2. MPH + self-help behavioural therapy model

Model overview

This model is comparing staying on MPH if you are a partial responder versus adding telephone assisted self-help behavioural therapy in children. The model is interested in the added value of a behavioural therapy on top of medication. The intervention involved parents reading 8 self-help booklets dealing with disruptive behaviour disorders and parenting that were mailed to them approximately every 2 weeks. Parents received 10 phone consultations of about 30 minutes each in the first 6 months, and then 4 booster calls during the second 6 months.

The population is children with ADHD who are on a stable dose of MPH, but had functional impairment (in the study this was functional impairment in at least one of the domains of the Weiss Functional Impairment Rating Scale). This can be seen as the baseline population because children are on MPH in both the intervention and the control group.

This is based on a single study reporting outcomes at 12 months. The GC thought that analysing the cost effectiveness of this study would be useful because it is an intervention they envisaged could be used as a baseline intervention in current practice because; it is more longer term than the usual courses of behavioural therapy, it involves self-help and telephone consultations. Although, as the intervention will be provided on an individual basis, the cost of the behavioural therapy is likely to be high.

The model is a decision tree model with a 1 year time horizon. Children enter the model being stable on methylphenidate, and can either remain on methylphenidate or add behavioural therapy. As the model is using a time horizon of 12 months and the trial data is also 12 months long – no assumptions need to be made beyond 12 months about what patients might then go on to.

Data

As mentioned above clinical data is based on a single study.[9] The only costs included in the model are the costs of the behavioural therapy, as any other costs are assumed to be common to the both arms. Utilities are also from the same source as the other models, with additional sources being tested in a sensitivity analysis. The utility gain from response is assumed to increase linearly over the trial period to reflect that the effect may not be immediate. The response probabilities are derived from analysis in Winbugs software which gave simulations of baseline and treatment response probabilities to use in the PSA.

Results

The probabilistic base case results showed the ICER of the intervention to be very high (£114,803). The additional benefit from the intervention cannot justify the additional cost of providing the intervention. It is a resource intensive intervention on top of medication because staff time spent on the phone is needed which means the intervention is provided on an individual basis.

A threshold analysis on costs showed that the cost of the intervention would have to be around 17% what it is in the base case to make the intervention cost effective, which is a significant reduction. This would equate to somewhere between two to three 30 minute phone calls. A threshold analysis on QALYs showed that the incremental QALY would need to go from 0.0076 to 0.0434 to make the intervention cost effective. Varying the time horizon found that the effect would have to be stable after the intervention ended up to at least 3 years to make the intervention cost effective. When varying both the time horizon and the utility gain simultaneously, this also showed that around 3.5 years at minimum (regardless of changes in utility gain) would be needed for the ICER to be under £20,000 per QALY. A 2-way sensitivity analysis varying both the baseline response probability and the intervention response relative risk showed that there is not any level of combination of baseline risk and relative risk that would make the intervention cost effective. Varying the utility values using different sources also showed that the model was sensitive to QALYs but the ICERs still remained high.

When assuming the effect increases linearly to 6 months (as the phone calls are more intense up until that point), and stays at that level until 12 months, as opposed to increasing linearly to 12 months; This showed that although the ICER fell, it was still above the NICE threshold because although there is a higher incremental QALY, this is still not high enough to justify the cost.

The results have to be interpreted with caution, because the model is only comparing the addition of a self-help non-pharmacological intervention on top of what was used as a baseline in the study (on MPH). It does not tell us about what else might be cost effective that a patient could add or switch to if they are a partial responder, only that what we have investigated as an addition is not cost effective. It also needs to be interpreted with caution as to whether the results can be extrapolated to other treatments that patients might only be partially responding to. But given the 2-way sensitivity analysis, we can be fairly confident that even another treatment with a higher baseline response rate or higher relative risk wold still not improve the ICER to a level considered cost effective.

This model is not without its limitations. It is only based on a single study. It can be difficult to also marry-up the conclusions of the model with what might be interpreted from the clinical review about the interventions in question. On a continuous scale, the improvements may be more subtle and there could still be an improvement in quality of life even if someone hasn't gone from non-response to response. For the study this model is based on (Dose 2016), the clinical review did not find the intervention clinically effective based on continuous outcomes (using the guideline cut-off of >20% of the control group risk). However, using the clinical review MID for dichotomous outcomes implies that the intervention has clinical benefit. Therefore the two outcomes are in conflict here. The committee opinion was that the clinical review in general is unlikely to have captured all the benefits of non-pharmacolgical treatment, because these are wider than just ADHD core symptoms. Other benefits also may not have been captured such as longer term impacts which are unknown, and the impact on other sectors. Structural assumptions keeping the model simple are also a limitation.

3. Medication + CBT model

Model overview

This model is comparing staying on medication if you are a partial responder versus adding (individual) CBT. The model is therefore interested in the added value of CBT on top of medication. The population are adolescents who are on a stable dose of medication for the last 2 months (medication is stated as an FDA approved medication for ADHD), but have clinically significant symptoms as rated by a CGI-S rating of 3 or above.

The intervention involved 12 sessions of individual CBT, and two additional parent only sessions were offered.

A with the previous models, the model is a decision tree model with a 1 year time horizon. Patients who enter the model are already on medication but have some clinically significant symptoms. Patients can either stay on their medication or add CBT on top of their medication. Outcomes are in terms of response or no response at the 4 month time-point because that was the length of the trial.

Data

This is based on a single study reporting outcomes at 4 months.[55]

The effect is extrapolated from 4 months to the end of the model (12 months). As the medication the adolescents are currently on is assumed to be the baseline or current practice, then this applies for the whole time horizon of the model. Everyone in the baseline arm of the model stays on the baseline for the whole time period regardless of whether they respond or not. It was decided to extrapolate the effects from the trial and not make further assumptions about what treatments people might go on to following the end of the trial period, as this would involve too many assumptions. It was felt that this would be a larger omission from a model that compared a drug to a non-drug comparison directly (like the ATX model), whereas here we are interested in the addition of an intervention to a common baseline. Because of the baseline applying to both arms it may also be argued that costs are likely to be similar for both arms even if people change treatments over time – unless they change to different treatments or at different times because of the intervention itself, but we had no information on this.

The response probabilities are derived from analysis in Winbugs software which gave simulations of baseline and treatment response probabilities to use in the PSA.

The only costs included in the model are the costs of CBT. The source for utility data is the same as has been used in all the models in this guideline. The utility gain from response is assumed to increase linearly over the trial period to reflect that the effect may not be immediate.

Results

The probabilistic base case results show that the addition of CBT is not cost effective (ICER of £62,007 per QALY). This is mostly down to the high cost of the intervention per person because it is individual rather than group format.

Various sensitivity analyses were conducted; one sensitivity analysis assumed that the effect of CBT diminishes and linearly decreases down from 4 months when the intervention ends to 12 months. This showed that the ICER increased to £105,192 per QALY because the incremental QALYs fell.

Threshold analyses showed that the number of sessions that would need to be provided to make the intervention cost effective would be between 3 and 4 – assuming the same level of effect. The incremental QALY between the intervention and comparison would need to be 0.0582 (base case 0.0188) to make the intervention cost effective. The time horizon of the model would also have to be almost 3 years to make the intervention cost effective, all other things being equal, again assuming the effect post treatment is maintained.

A 2-way sensitivity analysis varying both the baseline response probability and the intervention response relative risk showed that there is not any level of combination of baseline risk and relative risk that would make the intervention cost effective (assuming all other things the same like the base case cost). A 2-way sensitivity analysis varying both the time horizon of the model and the utility gain of responders over non-responders showed that the intervention is cost effective with a shorter time horizon if the incremental utility gain is

higher, as expected. Please see Appendix 2 for more details. Finally, varying the utility values using different sources also showed that the model was sensitive to QALYs but the ICERs still remained high.

The model needs to be interpreted with caution because it can only be inferred that the addition of individual CBT is not cost effective compared to staying on something that you are only partially responding to. It is not providing any information on what other treatments might be more cost effective. There are likely to be other treatments that are more cost effective than adding CBT.

Limitations include (which are very similar to those of the previous model); the model is only based on a single study with a small population. There is somewhat of a discord between the data that the models use and the data that the clinical review extracted. As mentioned in the limitations section of the previous model – it may be that the improvements on a continuous scale may be more subtle and there could still be an improvement in quality of life even if someone hasn't gone from non-response to response. From the clinical review using continuous outcomes; the study used in this model showed that the addition of individual CBT to mixed medication has a clinically important benefit. This agrees with the dichotomous outcome. Even though the two outcome types agree, it still remains that even though an intervention might be effective it isn't effective enough to make it cost effective. The committee opinion was that the clinical review in general is unlikely to have captured all the benefits of non-pharmacolgical treatment, because these are wider than just ADHD core symptoms. Other benefits also may not have been captured such as longer term impacts which are unknown, and the iimpact on other sectors. The structural assumptions the model has made about not including assumptions about further treatment can be seen as a limitation if in fact the addition of CBT has an impact on underlying resource use.

See Table 36, Table 37 and Table 38 for summaries of all three models.

1.6.5 Unit costs

Drug costs:

Relevant unit costs are provided below to aid consideration of cost-effectiveness. The drugs listed below are based on those identified from the clinical review as well as those commonly used even if the review did not find evidence on them, and therefore do not include the entire list of interventions from the protocol.

The costs below are illustrative. For the commonly used ADHD drugs; a low and high dose has been demonstrated and taken from the BNF. Some doses were not taken from the BNF and the reason for this is highlighted. Advice has also been taken from the BNF about whether a single dose per day or the doses can be divided, where available. For drugs that are not used for ADHD then the clinical review was used for dosing information.

Note that there can be various branded generic versions of a drug, but drugs of the same class with the same dose have the same cost in the drug tariff regardless of who manufactures it.

Table 39: UK costs of ADHD drugs for children

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source
Methylphenidate hydrochloride					
Methylphenidate immediate release	Low dose: 10mg per day	5mg tablet (pack of 30)	£6.14	£73.73	Dose: BNF Cost: BNF (DT

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source
		= £3.03			price)
Methylphenidate immediate release	High dose: 60mg per day	20mg tablet (pack of 30) = £10.92	£33.22	£398.58	Dose: BNF Cost: BNF (DT price)
Modified release tablet	Low dose: 18mg per day	18mg tablet (pack of 30) = £31.19	£31.62	£379.48	Dose: BNF Cost: BNF (DT price)
Modified release tablet	High dose: 54mg per day	54mg tablet (pack of 30) = £60.48	£61.32	£735.84	Dose: BNF Cost: BNF (DT price)
Modified release capsule	Low dose: 20mg per day	20mg capsule (pack of 30) = £30.00	£30.42	£365.00	Dose: BNF Cost: BNF (DT price)
Modified release capsule	High dose: 60 mg per day	60mg capsule (pack of 30) = £67.32	£68.26	£819.06	Dose: BNF Cost: BNF (NHS indicative price) (a)
Atomoxetine					
Capsule	Low dose: 40 mg per day	40mg capsule (pack of 28) = £53.09	£57.67	£692.07	Dose: BNF Cost: BNF (DT price)
Capsule	High dose: 100 mg per day	100mg capsule (pack of 28) = £70.79	£76.90	£922.80	Dose: BNF Cost: BNF (DT price)
Oral solution	High dose: 100 mg per day	4mg/1ml oral solution (300 ml) = £85	£215.45	£2,585.42	Dose: Using equivalent high tablet dose Cost: BNF (DT price)
Dexamfetamine					
Tablet	Low dose: 5mg per day	5mg tablet (pack of 28) = £21.53	£23.39	£280.66	Dose: BNF Cost: BNF (DT price)
Tablet	High dose: 20mg per day	10mg tablet (pack of 30) = £39.78	£80.67	£967.98	Dose: BNF Cost: BNF (DT price)
Oral solution	High dose: 20mg per day	5mg/5ml oral solution (500ml) = £114.49	£139.30	£1,671.55	Dose: Using equivalent high tablet dose Cost: BNF (DT price)
Lisdexamfetamine					
	Low dose: 20mg per day (b)	20mg capsule (pack of 28) = £54.62	£59.33	£712.01	Dose: guideline committee Cost: BNF (DT price)
	Low dose: 30mg per day	30mg capsule (pack of 28)	£63.27	£759.20	Dose: BNF Cost: BNF (DT

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source
		= £58.24			price)
	High dose: 70mg per day	70mg capsule (pack of 28) = £83.16	£90.34	£1,084.05	Dose: BNF Cost: BNF (DT price)
Other drugs (c)					
Guanfacine hydrochloride (modified release)	4mg per day	4mg tablet (pack of 28) = £76.16	£82.73	£992.80	Dose: Clinical review Cost: BNF (NHS indicative price)
Clonidine hydrochloride	400 micrograms per day (d)	100 microgram tablet (pack of 112) = £8.04	£8.73	£104.81	Dose: Clinical review Cost: BNF (DT price)
Risperidone	2mg per day	1mg tablet (pack of 20) = £0.80	£2.43	£29.20	Dose: Clinical review Cost: BNF (DT price)
Amantadine hydrochloride	150mg per day	100mg tablet (pack of 56) = £41.00	£33.40	£400.85	Dose: Clinical review Cost: BNF (DT price)
Melatonin (modified release)	6mg per day	2mg tablet (pack of 30) = £15.39	£46.81	£561.74	Dose: Clinical review Cost: BNF (DT price)
Bupropion hydrochloride (modified release)	150mg per day	150mg tablet (pack of 60) = £41.76	£21.17	£254.04	Dose: Clinical review Cost: BNF (DT price)
Modafinil	300mg per day	100mg tablet (pack of 30) = £5.88	£17.89	£214.62	Dose: Clinical review Cost: BNF (DT price)
Buspirone hydrochloride	30mg per day	10mg tablet (pack of 30) = £4.63	£14.08	£169.00	Dose: Clinical review Cost: BNF (DT price)
Aripiprazole	20mg per day	10mg tablet (pack of 28) = £2.77	£6.02	£72.22	Dose: Clinical review Cost: BNF (DT price)
Venlafaxine hydrochloride	75mg per day	37.5mg tablet (pack of 56) = £2.04	£2.22	£26.59	Dose: Clinical review Cost: BNF (DT price)

Source: BNF, October 2017.

(a) No drug tariff price available for the 60mg.

(b) A dose of 20mg is demonstrated here as committee opinion was that this is a dose that would be used in children, even though it is below the BNF starting dose.

(c) Guanfacine is the only drug from this list licensed for ADHD. It is less commonly used and is a newer drug so one example dose within the licensed range is demonstrated here. The doses of the other drugs below

guanfacine were taken from the clinical review as there was no information in the BNF about doses for this condition.

(d) Based on a dose from a trial of 8micrograms per kg and assuming a 50kg child (a conservative estimate of weight)

Table 40: UK costs of ADHD drugs for adults

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source of dose
Methylphenidate hydrochloride					
Methylphenidate immediate release	Low dose: 20mg per day	10mg tablet (pack of 30) = £5.49	£11.13	£133.59	Dose: BNF Cost: BNF (DT price)
Methylphenidate immediate release	High dose: 100mg per day	As above	£55.36	£664.30	Dose: BNF Cost: BNF (DT price)
Modified release tablet	Low dose: 36mg per day	36mg tablet (pack of 30) = £42.45	£43.04	£516.48	Dose: BNF Cost: BNF (DT price)
Modified release tablet	High dose: 108mg per day	54mg tablet (a) (pack of 30) = £60.48	£122.64	£1,471.68	Dose: BNF Cost: BNF (DT price)
Modified release capsule	Low dose: 20mg per day	20mg capsule (pack of 30) = £30.00	£30.42	£365.00	Dose: BNF Cost: BNF (DT price)
Modified release capsule	High dose: 100mg per day	50mg capsule (pack of 30) = £62.52	£126.78	£1,521.32	Dose: BNF Cost: BNF (NHS indicative price) (a)
Atomoxetine					
	Low dose: 40 mg per day	40mg tablet (pack of 28) = £53.09	£57.67	£692.07	Dose: BNF Cost: BNF (DT price)
	High dose: 100 mg per day	100mg tablet (pack of 28) = £70.79	£92.28	£1,107.36	Dose: BNF Cost: BNF (DT price)
Lisdexamfetamine dimesylate					
	Low dose: 30 mg per day	30mg tablet (pack of 28) = £58.24	£63.27	£759.20	Dose: BNF Cost: BNF (DT price)
	High dose: 70 mg per day	70mg tablet (pack of 28) = £83.16	£90.34	£1,084.05	Dose: BNF Cost: BNF (DT price)
Dexamfetamine sulfate					
	Low dose: 20mg per day	10mg tablet (pack of 30) = £39.78	£80.67	£967.98	Dose: BNF Cost: BNF (DT price)
	High dose: 60mg per day	20mg tablet (pack of 30) = £79.56	£161.33	£1,935.96	Dose: BNF Cost: BNF (NHS indicative price) (a)

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source of dose
Other drugs					
Guanfacine hydrochloride (modified release)	4mg per day	4mg tablet (pack of 28) = £76.16	£82.73	£992.80	Dose: Estimate based on children's dose Cost: BNF (NHS indicative price)
Bupropion hydrochloride (modified release)	300 mg per day	150mg tablet (pack of 60) = £41.76	£42.34	£508.08	Dose: Clinical review Cost: BNF (DT price)
Reboxetine (Edronax)	8mg per day	4mg tablet (pack of 60) = £18.91	£19.17	£230.07	Dose: Clinical review Cost: BNF (DT price)
Venlafaxine hydrochloride	225 mg per day	37.5mg tablet (pack of 56) = £2.04	£6.65	£79.78	Dose: Clinical review Cost: BNF (DT price)

Source: BNF, October 2017.
(a) No BNF drug tariff price for this dose yet.

The pricing structure of the different drugs can also impact the overall cost, as if you are taking a higher dose and you could do this once a day, then a higher dose tablet tends to be cheaper than taking two tablets of half the dose. So with most drugs there are economies of scale of the higher formulations. This isn't always the case though. With some drugs it is possible to take only one tablet a day, such as the modified release versions, but with others you would need to take tablets at multiple points in the day, which means more pills per day of lower formulations.

Costs of other healthcare resource such as hospital appointments that may differ by intervention are illustrated below.

Other resource use

Table 41: Staff costs associated with selecting and monitoring medication treatment

Staff	Costs	Source
Psychiatric Consultant	£106 per hour	PSSRU 2016
Band 5 nurse	£36 per hour	PSSRU 2016

For example, people on stimulants may see healthcare professionals more frequently in the beginning in order to make sure the dose is appropriate and then may see healthcare professionals less frequently.

Non pharmacological treatment costs:

Highlighted below are some costs associated with non-pharmacological treatment. Table 41 shows the costs of individual staff that may be providing treatment such as behavioural therapy/cognitive behavioural therapy

Costs can vary depending on the band of person providing the treatment. It is also common for the clinician to have an assistant to help with the administration and setting up of the training. The relevant bands for the respective roles were derived from the guideline committee when identifying the inputs for the parent training model.

Table 42: Staff costs associated with behavioural therapy

Staff	Costs	Source
Clinical psychologist (Band 8a, clinical psychologist principal (community based))	£62 per hour	PSSRU 2016
Band 4 assistant	£30 per hour	PSSRU 2016

The total costs of a course of treatment per person depend upon the number of sessions, whether it is a group or individual course, how much preparation is needed, the band of staff involved, and also the individual components that might make up the course (e.g. if training is also provided for family members/teachers (if children)).

Published costs:

Some illustrations of specific costs of behavioural therapy training are provided below from the PSSRU;

Table 43: Published PSSRU costs on cognitive behavioural treatments

Intervention	Details	Costs	Source
Cognitive Behavioural Therapy for adolescents (individual). (a)	Length of contact; 55 minutes (average duration of sessions)	£97 per CBT session	PSSRU 2016
Mindfulness based cognitive therapy – group based intervention for adults. (b)	Therapy sessions lasted 2 hours with 12 people attending each session.	£52 per hour of non-direct contact, £86 per hour of direct contact, £173 per session, £14 per service user (=£173/12 people)	PSSRU 2016

(a) This cost is based on costs estimated for a randomised controlled trial of interventions for adolescents with depression. The setting was two Child and Mental Health Services (CAMHS) teams in secondary care where CBT was delivered.

(b) Mindfulness-based cognitive therapy (MBCT) is a manualised skills training programme designed to enable patients to learn skills that prevent the recurrence of depression. It is derived from mindfulness-based stress reduction, a programme with proven efficacy in ameliorating distress in people suffering chronic disease. To provide the unit costs of this service, we have drawn on information provided by Kuyken et al. (2008) which was based on data from three mindfulness-based cognitive therapy therapists who took part in the study. There were 12 individuals in each group.

1.7 Resource impact

We do not expect recommendations resulting from this review area to have a significant impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

Children and young people aged 5 to 18

Atomoxetine versus PT/FT

- No evidence for quality of life, clinical global impression scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality) and clinical global impressions scale (PT; 1 study very low quality).
- There was no clinically important benefit for ADHD symptoms total (PT parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality), ADHD hyperactivity symptoms (PT teacher rated; 1 study very low quality) and ADHD inattention symptoms (PT parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality).

Stimulants versus Exercise

- No evidence for quality of life, ADHD symptoms total, clinical global impression scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality) and ADHD inattention symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study moderate quality).

Stimulants versus NF

- No evidence for quality of life, clinical global impression scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality) and ADHD inattention symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality).
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality) (FU teacher rated; 1 study very low quality), ADHD hyperactivity symptoms (PT teacher rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT self-rated; 2 studies very low quality) (FU self-rated; 1 study very low quality), ADHD inattention symptoms (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (FU teacher rated; 1 study very low quality) (PT self-rated; 1 study very low quality) (FU self-rated; 1 study very low quality) and academic performance (PT self-rated; 1 study very low quality) (FU self-rated; 1 study very low quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality) (FU teacher rated; 1 study very low quality), ADHD inattention symptoms (PT teacher rated; 1 study very low quality) (PT self-rated; 1 study very low quality) and academic performance (PT self-rated; 1 study very low quality).

Stimulants + NSST versus stimulants

- No evidence for quality of life, ADHD symptoms total, ADHD inattention symptoms, clinical global impression scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT teacher rated; 1 study very low quality) (FU teacher rated; 1 study very low quality).
- There were no clinically important benefits for ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality).

Mixed medication versus PT/FT

- No evidence for quality of life, clinical global impression scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT teacher rated; 1 study low quality) (PT parent rated; 1 study low quality) (PT observer rated; 1 study low quality) and ADHD inattention symptoms (PT teacher rated; 1 study low quality).
- There were no clinically important benefits for ADHD symptoms total (FU teacher/parent rated; 1 study moderate quality), ADHD inattention symptoms (PT parent rated; 1 study low quality), numeracy outcomes (PT observer rated; 2 studies very low to moderate quality) and literacy outcomes (PT observer rated; 2 studies very low to moderate quality) (FU observer rated; 1 study moderate quality).

Combination versus non-pharmacological treatment in children and young people

Atomoxetine + PT/FT versus PT/FT

- No evidence for quality of life, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT teacher rated; 1 study low quality), ADHD hyperactivity symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality), ADHD inattention symptoms (PT teacher rated; 1 study low quality) and clinical global impression scale (PT; 1 study low quality).
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study low quality) and ADHD inattention symptoms (PT parent rated; 1 study low quality).

Atomoxetine + PE versus PE

- No evidence for clinical global impression scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for quality of life (PT parent rated; 1 study moderate quality), ADHD symptoms total (PT parent rated; 1 study high quality), ADHD hyperactivity symptoms (PT parent rated; 1 study high quality), ADHD inattention symptoms (PT parent rated; 1 study high quality) and academic outcomes (PT parent rated; 1 study moderate quality).

Atomoxetine + CBT versus CBT

- No evidence for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT self-rated; 1 study low quality).
- There was a clinically important harm for ADHD symptoms total (PT parent rated; 1 study low quality) and clinical global impressions scale (PT; 1 study very low quality).

Stimulants + NF versus NF

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT self-rated; 1 study very low quality), ADHD inattention symptoms (FU teacher rated; 1 study very low quality) and academic outcomes (PT self-rated; 1 studies very low quality).

- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality) (FU teacher rated; 1 study very low quality), ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality) (FU teacher rated; 1 study very low quality) (FU self-rated; 1 study very low quality), ADHD inattention symptoms (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT self-rated; 1 study very low quality) (FU self-rated; 1 study very low quality) and academic outcomes (FU self-rated; 1 study low quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (PT self-rated; 1 study very low quality), ADHD inattention symptoms (PT teacher rated; 1 study very low quality) (PT self-rated; 1 study very low quality) and academic outcomes (PT self-rated; 1 study very low quality).

Stimulants + CBT versus CBT

- No evidence for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT observer rated; 1 study high quality).

Mixed medication + PT/FT versus PT/FT

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT teacher rated; 1 study low quality) (PT observer rate; 1 study low quality) and ADHD inattention symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality).
- There were no clinically important benefits for ADHD symptoms total (FU teacher/parent rated; 1 study moderate quality), numeracy outcomes (PT observer rated ; 2 studies very low to low quality), literacy outcomes (PT observer rated; 2 studies very low to moderate quality) (FU observer rated; 1 study moderate quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (PT parent rated; 1 study moderate quality).

Combination versus pharmacological treatment in children and young people

Atomoxetine + PT/FT versus atomoxetine

- No evidence for quality of life, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, numeracy outcomes and literacy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT teacher rated; 1 study very low quality).
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study very low quality), ADHD hyperactivity symptoms (PT parent rated; 2 studies very low quality) (PT teacher rated; 2 studies very low quality), ADHD inattention symptoms (PT parent rated; 2 studies very low quality) (PT teacher rated; 2 studies very low quality), clinical global impression scale (PT; 2 studies very low quality) and behaviour outcomes (PT teacher rated; 1 study very low quality).

Stimulants + PT/FT versus stimulants

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, numeracy outcomes and literacy outcomes.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT teacher rated; 1 study very low quality).
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 3 studies low quality) (FU parent rated; 1 study low quality) (PT teacher rated; 2 1 study low quality), ADHD hyperactivity symptoms (PT parent rated; 2 studies moderate quality) (FU parent rated; 1 study very low quality) (FU teacher rated; 1 study very low quality), ADHD inattention symptoms (PT parent rated; 1 study low quality) and behavioural outcomes (PT parent rated; 1 study low quality).

Stimulants + PT/FT versus stimulants + NSST

- No evidence for quality of life, ADHD symptoms total, ADHD inattention symptoms, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT teacher rated; 1 study low quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (FU teacher rated; 1 study very low quality).

Stimulants + attention/memory/cognitive training versus stimulants

- No evidence for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study low quality).

Stimulants + NF versus stimulants

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality), (PT teacher rated; 1 study very low quality).
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality) (FU teacher rated; 1 study very low quality), ADHD hyperactivity symptoms (FU parent rated; 1 study very low quality) (FU teacher rated; 1 study very low quality) (PT self-rated; 1 study very low quality) (FU self-rated; 1 study very low quality), ADHD inattention symptoms (PT parent rated; 1 study very low quality) (FU parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality) (FU teacher rated; 1 study very low quality) (PT self-rated; 2 studies very low quality) (FU self-rated; 1 study very low quality) and academic outcomes (PT self-rated; 1 study very low quality) (FU self-rated; 1 study very low quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (PT self-rated; 1 study very low quality) and academic outcomes (PT self-rated; 1 study very low quality).

Mixed medication + PT/FT versus mixed medication

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events and minor adverse events.

- There were no clinically important benefits for ADHD symptoms total (FU parent rated; 1 study very low quality) (FU teacher/parent rated; 1 study moderate quality), ADHD hyperactivity symptoms (PT teacher rated; 3 studies very low to moderate quality) (FU parent rated; 1 study low quality), ADHD inattention symptoms (PT parent rated; 1 study moderate quality) (PT teacher rated; 1 study moderate quality) (FU parent rated; 1 study very low quality), behavioural outcomes (PT teacher rated; 2 studies very low quality), emotional dysregulation (PT teacher rated; 1 study very low quality), numeracy outcomes (PT; 2 studies very low to moderate quality), literacy outcomes (PT; 2 studies very low to moderate quality) (FU; 1 study moderate quality) and academic outcomes (PT teacher rated; 2 studies very low quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (PT parent rated; 1 study moderate quality) (PT observer rated; 1 study low quality) and emotional dysregulation (PT teacher rated; 1 study very low quality).

Mixed medication + CBT versus mixed medication

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT self-rated; 2 studies low to moderate quality) (PT parent rated; 2 studies low to moderate quality), ADHD hyperactivity symptoms (PT self-rated; 1 study low quality) (PT parent rated; 1 study low quality) and ADHD inattention symptoms (PT self-rated; 1 study low quality) (PT parent rated; 1 study low quality).

Mixed medication + PE versus mixed medication + NSST

- No evidence for quality of life, ADHD symptoms total, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse event and literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT parent rated; 1 study low quality) and ADHD inattention symptoms (PT parent rated; 1 study low quality) (FU parent rated; 1 study low quality).
- There were no clinically important benefits for ADHD hyperactivity symptoms (FU parent rated; 1 study low quality), behavioural outcomes (PT parent rated; 1 study low quality) (FU parent rated; 1 study low quality) and emotional dysregulation (PT parent rated; 1 study moderate quality) (FU parent rated; 1 study low quality).

Mixed medication + sleep intervention versus mixed medication

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 2 studies very low quality) (PT teacher rated; 2 studies low quality), ADHD hyperactivity symptoms (PT teacher rated; 2 studies very low to low quality) (PT parent rated; 2 studies very low quality), ADHD inattention symptoms (PT parent rated; 2 studies very low quality) (PT teacher rated; 2 studies low quality) and behavioural outcomes (PT teacher rated; 2 studies very low to low quality).

Mixed medication + NF versus mixed medication

- No evidence for quality of life, ADHD hyperactivity symptoms, ADHD inattention symptoms, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT teacher rated; 1 study low quality) and behavioural outcomes (PT parent rated; 1 study low quality).

Combination versus no treatment/usual care in children and young people

Atomoxetine + PT/FT versus placebo/usual care

- No evidence for quality of life, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality), ADHD hyperactivity symptoms (PT parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality), ADHD inattention symptoms (PT parent rated; 1 study very low quality) (PT teacher rated; 1 study very low quality) and clinical global impressions scale (PT; 1 study very low quality).

Mixed medication + PT/FT versus placebo/usual care

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures and emotional dysregulation.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT teacher rated; 1 study low quality) and ADHD inattention symptoms (PT parent rated; 1 study low quality) (PT teacher rated; 1 study low quality).
- There were no clinically important benefits for ADHD symptoms total (PT teacher/parent rated; 1 study moderate quality), ADHD hyperactivity symptoms (PT observer rated; 1 study moderate quality), numeracy outcomes (PT observer rated; 2 studies very low to moderate quality) and literacy outcomes (PT observer rated; 2 studies very low to low quality) (FU observer rated; 1 study moderate quality).
- There was a clinically important harm for ADHD hyperactivity symptoms (PT parent rated; 1 study low quality).

Combination versus other combined treatments in children and young people

Stimulants + NF versus stimulants + attention/memory/cognitive training

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, emotional dysregulation, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD inattention symptoms (FU teacher rated; 1 study high quality).
- There were no clinically important benefits for ADHD symptoms total (PT parent rated; 1 study moderate quality) (PT teacher rated; 1 study moderate quality) (FU parent rated; 1 study moderate quality) (FU teacher rated; 1 study moderate quality), ADHD hyperactivity symptoms (PT parent rated; 1 study moderate quality) (PT teacher rated; 1 study moderate quality) (FU parent rated; 1 study moderate quality) (FU teacher rated; 1 study moderate quality) and ADHD inattention symptoms (PT parent rated; 1 study moderate quality) (PT teacher rated; 1 study moderate quality) (FU parent rated; 1 study moderate quality).

Adults over the age of 18

Pharmacological treatment versus non-pharmacological treatment in adults

Stimulants + NSST versus CBT

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT self-rated; 1 study low quality) (PT observer rated; 1 study low quality), ADHD hyperactivity symptoms

(PT observer rated; 1 study low quality), ADHD inattention symptoms (PT observer rated; 1 study moderate quality) and emotional dysregulation (PT self-rated; 1 study moderate quality).

Combination versus non-pharmacological treatment in adults

Stimulants + CBT/DBT versus CBT/DBT alone

- No evidence for quality of life, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT self-rated; 1 study low quality) (PT observer rated; 1 study moderate quality) and clinical global impressions scale (FU; 1 study high quality).
- There were no clinically important benefits for ADHD symptoms total (PT self-rated; 1 study low quality) (PT observer rated; 2 studies low quality), ADHD hyperactivity symptoms (PT observer rated; 1 study low quality), ADHD inattention symptoms (PT observer rated; 1 study low quality), emotional dysregulation (PT; 2 studies moderate quality) and clinical global impressions scale (PT; 1 study low quality).
- There was a clinically important harm for ADHD symptoms total (PT self-rated; 1 study low quality).

Stimulants + CBT/DBT + PT/FT versus NSST + PT/FT alone

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD hyperactivity symptoms (PT observer rated; 1 study low quality).
- There were no clinically important benefits for ADHD symptoms total (PT observer rated; 1 study low quality), ADHD inattention symptoms (PT observer rated; 1 study low quality), child ADHD symptoms total (PT parent rated; 1 study low quality) and emotional dysregulation (PT parent rated; 1 study moderate quality).

Combination versus pharmacological treatment in adults

Stimulants + CBT/DBT versus stimulants + NSST alone

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT self-rated; 1 study moderate quality) (PT observer rated; 1 study moderate quality), ADHD hyperactivity symptoms (PT observer rated; 1 study moderate quality), ADHD inattention symptoms (PT observer rated; 1 study moderate quality) and emotional dysregulation (PT; self-rated 1 study moderate quality).

Mixed medication + CBT/DBT versus mixed medication alone

- No evidence for discontinuation due to side effects, serious adverse events, minor adverse events, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for ADHD symptoms total (PT observer rated; 1 study low quality) (PT self-rated; 3 studies very low quality) (FU self-rated; 2 studies very low quality), ADHD hyperactivity symptoms (FU self-rated; 2 studies very low quality), ADHD inattention symptoms (PT self-rated; 2 studies very low quality)(FU self-rated; 2 studies very low quality), clinical global impressions scale (PT; 1 study low quality), emotional dysregulation (PT observer rated; 1 study low quality) (PT self-rated; 1 study very low quality) (FU self-rated; 1 study low quality) and behavioural outcomes (FU; 1 study very low quality).

- There were no clinically important benefits for quality of life (PT; 1 study very low quality) (FU; 1 study very low quality), ADHD hyperactivity symptoms (PT self-rated; 2 studies very low quality) and behavioural outcomes (PT; 1 study very low quality).

Mixed medication + CBT/DBT versus mixed medication + NSST

- No evidence for discontinuation due to side effects, serious adverse events, minor adverse events, behavioural outcomes, literacy outcomes and numeracy outcomes.
- There was a clinically important benefit for clinical global impressions scale (PT; 1 study very low quality).
- There were no clinically important benefits for quality of life (PT; 1 study low quality), ADHD symptoms total (PT self-rated 2 studies very low quality) (FU self-rated 1 study very low quality), ADHD hyperactivity symptoms (PT self-rated; 1 study very low quality), ADHD inattention symptoms (PT self-rated; 1 study very low quality) and emotional dysregulation (PT self-rated; 1 study very low quality).

Combination versus no treatment/usual care in adults

Stimulants + CBT/DBT compared to NSST alone

- No evidence for quality of life, clinical global impressions scale, discontinuation due to side effects, serious adverse events, minor adverse events, behavioural measures, literacy outcomes and numeracy outcomes.
- There were no clinically important benefits for ADHD symptoms total (PT self-rated; 1 study low quality) (PT observer rated; 1 study low quality), ADHD hyperactivity symptoms (PT observer rated; 1 study low quality), ADHD inattention symptoms (PT observer rated; 1 study low quality) and emotional dysregulation (PT self-rated; 1 study moderate quality).

1.8.2 Health economic evidence statements

CG72 evidence

- One cost-utility analysis found that medication + individual CBT was not cost effective compared to medication alone, for treating ADHD in adults on medication but with clinically significant symptoms (ICER: £65,279). This analysis was assessed as directly applicable with potentially serious limitations.

Update guideline evidence

- One original cost-utility analysis found that behavioural therapy was cost effective (had the highest net benefit) compared to atomoxetine, and a combination of behavioural therapy and atomoxetine, for treating ADHD in children. This analysis was assessed as directly applicable with potentially serious limitations.
- One original cost-utility analysis found that Methylphenidate + self-help behavioural therapy was not cost effective compared to methylphenidate alone, for treating ADHD in children on methylphenidate but with functional impairment (ICER: £114,803). This analysis was assessed as directly applicable with potentially serious limitations.
- One original cost-utility analysis found that medication + individual CBT was not cost effective compared to medication alone, for treating ADHD in adolescents on medication but with clinically significant symptoms (ICER: £62,007). This analysis was assessed as directly applicable with potentially serious limitations.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The committee considered quality of life, ADHD symptoms and CGI assessment of response to be critical outcomes. ADHD symptoms were separately considered as total, hyperactivity and inattention subscales. The committee did not prioritise any one subscale. ADHD symptoms were separately considered when reported by self, parent, teacher and investigator. The committee considered that all had their merit but that symptoms reported by teacher or investigator were likely to be the most objective assessment of effect.

The committee considered intervention related discontinuations, serious adverse events, behavioural/functional measures, emotional dysregulation and academic outcomes to be important outcomes.

1.9.1.2 The quality of the evidence

The committee noted that the body of evidence for this review was typically low or very low quality. There was no evidence in children under the age of 5 for this review. There was a larger body of evidence for children aged 5 to 18 than for adults over the age of 18. While there were a large number of studies meeting the criteria for the review, in general they were small studies providing imprecise results and only single studies per outcome.

The overall objective of the review was to compare the broad strategies of pharmacological and non-pharmacological interventions both for ADHD symptoms and behaviour, either in isolation or combination. As the committee agreed that different interventions under the headings of pharmacological and non-pharmacological may well have different effects, as established by the separate specific pharmacological and non-pharmacological reviews, these were kept separate. However it was difficult to determine whether or not conflicting results reported by two or more studies related specifically to the interventions under investigation or other factors that differed between trials (for example the exact previous treatment and response of the participants, the quality and content of usual care).

The committee noted that behavioural outcomes, on which one might expect non-pharmacological interventions to have a greater impact such as the outcomes focusing on behaviour and emotional dysregulation, were less commonly reported than ADHD symptom outcomes.

The committee noted that it is much more challenging to provide a true active control arm for non-pharmacological interventions compared with the use of placebo for pharmacological interventions, therefore the trials included in these reviews were rarely if ever blinded to the non-pharmacological intervention allocation.

The committee acknowledged that these limitations in the design of non-pharmacological treatments could impact on the interpretation of the effectiveness of non-pharmacological treatments.

The committee agreed that the quality of the evidence in the review was not sufficient to make strong recommendations about specific combinations of any interventions.

1.9.1.3 Benefits and harms

Overall (and children aged 5 to 18)

Overall the committee agreed that the evidence supported the following statements. Direct comparisons of pharmacological treatment with non-pharmacological treatment showed a

benefit for pharmacological treatment, principally in terms of ADHD symptoms. Combined treatments showed a benefit in ADHD symptoms over either pharmacological treatment or non-pharmacological treatment in isolation, this benefit was larger and more consistently observed when compared with non-pharmacological treatment, although the benefit did not consistently equate to a clinically important difference as per the committee's previously agreed thresholds. Combined treatments showed a benefit in ADHD symptoms compared to no active intervention or usual care. No comparison between any two combined treatments showed a clear picture of consistent clinically important benefit. The committee noted that although the above was an appropriate summary of the evidence, there were many comparisons showing no clinical difference and relatively frequent inconsistencies across the evidence base.

The benefits from the HE modelling were as follows: in the child atomoxetine combination model, total QALYS were as follows; behavioural therapy: 0.773, Atomoxetine: 0.790, combination treatment: 0.794. In the child methylphenidate + self-help behavioural therapy model, total QALYs were 0.7648 in the intervention arm (combination), and 0.7573 in the comparator arm. In the adolescent CBT combination model, total QALYs were 0.7748 in the intervention arm (combination), and 0.7561 in the comparator arm.

The committee noted that although it was not entirely clear from the evidence base, theoretically non-pharmacological treatments and pharmacological treatments are likely to be effective at targeting different aspects of ADHD. Pharmacological treatments may be better for treating the core symptoms of ADHD whereas non-pharmacological treatments may be more beneficial for improving the functional status of people with ADHD.

Before considering whether any treatment at all is necessary for ADHD symptoms, the committee recommended that appropriate environmental modifications were in place – in some situations this may be all that is required to address the impact of milder ADHD symptoms.

The committee noted that any treatment choice for ADHD is associated with potential harms. Drugs are often considered to be 'more harmful' (see the pharmacological adverse events review for more detail on specific adverse effects of various drug options), however non-pharmacological treatments may have specific harms of their own (for example for people who feel stigmatised by having to undergo parent training) and if a person's treatment choice is not optimised to reduce their ADHD symptoms, there is harm from under treatment.

Children under the age of 5

There was no evidence identified in this review for this population. The committee agreed that the effects seen in children aged 5 to 18 were likely to be similar in the under 5 age group, however the committee noted that concerns around the adverse effects of medication in this younger age group.

Adults aged over 18

The committee noted that the studies in the combination review and non-pharmacological review in this age group focused heavily on CBT. CBT was specifically recommended in the previous guideline as the non-pharmacological intervention of choice in adults with ADHD. The non-pharmacological review supported the finding that CBT had a benefit for ADHD symptoms when compared with no intervention or usual care. However both reviews showed little difference between CBT and a non-specific supportive therapy. The committee was keen to emphasise that this did not imply a lack of efficacy of CBT and noted that the non-specific supportive therapies typically involved regular periods of face to face counselling. The committee agreed that this suggested that CBT is effective but that for some people, it may be possible to achieve similar benefits with structured programs that do not necessarily adhere to the principles of CBT.

Subgroups

There was insufficient evidence in this review to inform specific recommendations about subgroups of people with ADHD, either based on the severity of their symptoms or on any co-existing disorders.

Given the health economic evidence and the previous guideline recommendations, the committee agreed that it was appropriate to make consensus based recommendations on which groups may benefit from a combined approach. In children and young people, the committee supported the recommendations from the NICE guideline on antisocial behaviour and conduct disorders in children and young people, in which the families of all children with or at high risk of developing ODD/CD should be offered group parent training programmes.

Previous recommendations differentiated between children with mild or moderate ADHD and severe ADHD and suggested different strategies for the two groups. These recommendations were purely consensus based as no evidence existed to support that differentiation. In this update, again no evidence was found to support a differential strategy based on severity. However again the committee's consensus view was that medication should be reserved for those in whom ADHD was having significant impairment on their life. The committee agreed that as short term adverse effects of medication are well reported compared to other treatment approaches it is difficult to compare harms across treatments, but they are present in people that take medication (as documented in evidence report D on pharmacological safety) and healthcare professionals should only be offering medication to children in whom the risk benefit balance supported this decision. To achieve this aim, the committee recommended that medication should be first line treatment for those in whom environmental modifications had not reduced the impact of ADHD symptoms on at least one area of a child or adults' everyday life. This categorisation differs from the previous guideline's use of 'severe ADHD' and the committee agreed it was appropriate to focus more on the impact of symptoms as opposed to a diagnostic assessment of severity of disease. Addressing persistent symptoms in one domain is important in this age group, for example, parent/carer training and environmental modification may have reduced impairment in situations and relationships at home but not at school, it is important that the impairment at school is addressed to ensure the child or young person is has the best opportunity to achieve at school.

The committee noted that much of the evidence in this review on atomoxetine in children came from a study specifically looking at children with ADHD and ASD. Few of the pooled comparisons included this evidence but where this was the case – there was no obvious heterogeneity to support a different treatment effect in this population compared to the general population..

1.9.2 Cost effectiveness and resource use

No published economic evidence was identified for this question. Four studies included as economic evidence for this question in the previous guideline have been selectively excluded for reasons of applicability and methodological quality.

The previous guideline conducted two original economic models looking at combination treatments versus individual treatments, one in children and one in adults. The child model has been selectively excluded because it was based on two studies not included in the clinical review, it is however also superseded by three new models on combinations in children. The adult model is included in this update because no new modelling has been undertaken for adults as it was not felt to add value or change the conclusions of the previous model. A summary of the existing adult combination model and new children models can be found below.

The previous model in adults was in a population of adults with ADHD who are stable on medication but have clinically significant symptoms, and compared adding CBT to medication versus staying on medication alone. It was a decision tree model with a 1 year time horizon based on two short terms trials for clinical effect. This found that the addition of CBT was not cost effective with an ICER of £65,279 per QALY. This analysis was rated as directly applicable with potentially serious limitations, such as only based on two trials, extrapolation of effect, and only included intervention costs.

New health economic analysis – Atomoxetine combination model:

The previous child model was updated because it was expected there would be new data in children, and the combination questions have economic implications in terms of the trade-off between two interventions together having a large resource impact weighed up against whether the additional effect is enough to make them cost effective. It was discussed whether the effects of two different types of interventions were expected to be additive, and this was not believed to be the case, therefore even if pharmacological treatment is cost effective compared to doing nothing, and non-pharmacological treatment is cost effective compared to doing nothing; we cannot make the assumption that both together would therefore be cost effective. Only dichotomous outcomes could be used for a model to link to quality of life, which automatically reduces the pool of studies that can be used from the clinical review. The studies that had dichotomous outcomes had comparisons that the committee felt couldn't be combined, particularly around the differences in behavioural treatments for example it would not be appropriate to combine parent training with CBT. This is why the previous child model is being superseded by 3 models.

The first child model compared atomoxetine in combination with behavioural therapy (group parent training), to atomoxetine alone and behavioural therapy alone. This was a decision tree model with a one year time horizon. The population was mixed in terms of some children in the trials having treatment before, but none selected people specifically who were previous non-responders (or responders). Patients could withdraw from adverse events of atomoxetine and the model also included tolerable adverse events that had a utility decrement but treatment continued. Resource use of drugs and behavioural therapy were elicited from the committee. Clinical effectiveness was from 3 studies and these were combined in a network meta-analysis for the model. The probabilistic results showed behavioural therapy was the most cost effective. This was the cheapest and also the least effective intervention, but had the highest net benefit because the ICERs (when comparing an intervention to the next cheapest) were above the NICE £20,000 threshold (Atomoxetine compared to behavioural therapy: £44,175 per QALY, and combination treatment compared to Atomoxetine: £56,219 per QALY). Atomoxetine is more costly than behavioural therapy because of the ongoing monitoring required for each child, whereas the cost of behavioural therapy is spread over a group of children and is only for a short time frame. A sensitivity analysis using individual behavioural therapy costs showed that atomoxetine dominated behavioural therapy, and atomoxetine was the most cost effective compared to combination treatment. Another sensitivity analysis made assumptions about the effect of behavioural therapy diminishing after the treatment duration (10 weeks) and going down to zero by the end of the model (whereas in the base case the responders were assumed to remain responders for the whole time horizon), behavioural therapy still had the highest net benefit. Using different sources of utility values that derived utilities in different ways (such as direct valuation of health states, and using another generic measure instead of the EQ-5D) also did not lead to a different result. This was done to reassure the GC about the sensitivity of the EQ-5D, which it was debated is perhaps inappropriate for this condition, but there is no empirical evidence to support this. This analysis was assessed as directly applicable with potentially serious limitations. This is because it is only based on a small number of trials, no assumptions were made about further lines of treatment and so the costs and QALYs may be being underestimated because a non-responder will most likely find other treatments that work for them to accrue QALYs and costs. Also, the committee highlighted that the

effectiveness of non-pharmacological treatments is not well captured in trials and may be underestimated.

New health economic analysis – Methylphenidate + self-help telephone BT model:

The second model compared methylphenidate with the addition of telephone self-help behavioural therapy versus methylphenidate alone, in a population of children who are partial responders to methylphenidate (i.e. from the single clinical study used for effect this is specifically children who are stable on methylphenidate but have some functional impairment). This was a decision tree model with a 1 year time horizon. The clinical study used for effect had 12 month outcomes. No adverse events or costs of methylphenidate were included because this was the baseline common to both arms. Only intervention costs of the behavioural therapy were included. Probabilistic results showed that the addition of the behavioural therapy was highly cost ineffective (ICER = £114,803 per QALY). The incremental cost was high because this is an individual therapy. The incremental QALY was also small because the difference in response probabilities between the comparisons was quite small. Threshold analyses showed that the cost of the intervention would have to be significantly smaller to make the intervention cost effective. See appendix 2 for further detail on other threshold analyses undertaken. A 2-way sensitivity analysis varying the treatment effect and baseline probability showed that no combination of baseline and treatment effect would make the intervention cost effective, all other things being equal. As with the previous model, different utility sources were used, and the effect increased linearly to 6 months and remained at that level (as the phone calls were more intense up to that point) rather than increasing linearly to 12 months. Neither of these sensitivity analyses changed the conclusions. This analysis was assessed as directly applicable with potentially serious limitations. Similarly to the last model; effect is only based on a small sample of data – one study, effect could have been underestimated, and the structure has been kept simple.

New health economic analysis – medication + CBT model:

The third model compared medication with the addition of individual CBT versus medication alone. This was in a population of adolescents who were stable on medication but had some clinically significant symptoms. This was a decision tree model with a 1 year time horizon. No adverse events or costs of medication were included because this was the baseline common to both arms. Only intervention costs of CBT were included. The effectiveness of the comparisons was informed by a single study with trial duration of 4 months. Probabilistic results showed that the addition of the individual CBT was not cost effective (ICER = £62,007 per QALY) the incremental cost was again high because the intervention is individual and consists of 12 sessions. The cost of the intervention would need to be below around 32% of the base case cost to make the intervention cost effective. This equates to around 3 to 4 sessions or about 6 hours of CBT. The time horizon of the mode would need to be around 3 years to make the intervention cost effective. A 2-way sensitivity analysis of baseline and treatment effect showed that only with a very low baseline risk and very high treatment effect would the intervention be cost effective. If we also assume the effect of the treatment is not maintained the ICER becomes even larger (£105,192 per QALY). This analysis was assessed as directly applicable with potentially serious limitations. As with the previous models; effect is based on a single study, the effect may be being underestimated because trials are not good at capturing wider outcomes that CBT would address, the structure of the model is kept simple and so costs and effects may be being underestimated.

Children under the age of 5

See the non-pharmacological review and rationale for more information about recommendations in this age group. As a summary; medication is not recommended for this age group. The age of the children are considered too young to be medicated. A sensitivity analysis of the parent training model using a study in the under 5 group showed parent training to be cost effective in a group. Combinations are also not recommended in this group.

Children and young people aged over 5

Taking all the three models for children together, it can be concluded that it is uncertain if combination treatments (meaning combinations of pharma and non-pharma) are cost effective, because of their costs and also uncertainty about their treatment effect. If the behavioural therapy component is provided in a group, then this lowers the cost, which can have an impact on the result (this is more applicable however to parent training than it is to CBT – which is usually individual). However this is highly dependent on the treatment effect. The models need to be interpreted carefully because of the specific populations they are in; i.e. the implication in the second and third model is that a combination is being offered second line as they are partial responders to a drug, and also because they are on different drugs it needs to be taken into consideration with a consensus committee view about the ordering of treatments in the pathway. Additionally there is uncertainty as to whether results might be generalisable to other drugs for example.

This review was also about non-pharmacological treatments compared to pharmacological treatments. The only information on cost effectiveness available to us here is the comparison of atomoxetine versus behavioural therapy from the atomoxetine model. This showed that if we assume the effect of behavioural therapy continues, then atomoxetine is not cost effective compared to behavioural therapy. The drug price would have to be very small for atomoxetine to be cost effective because the costs of monitoring a drug far outweigh the costs of the behavioural therapy. If the effect is not maintained after the course has ended then atomoxetine becomes closer to being cost effective. But if the behavioural therapy is individual rather than a group then behavioural therapy is dominated by atomoxetine. However we haven't included the costs of further treatment to see how this impacts the results, because less people respond on behavioural therapy so a higher proportion of that cohort may end up on more expensive treatments later on, and titrating and monitoring the effect of a drug is resource intensive. So there are downstream trade-offs that we haven't been able to account for. It is accepted that pharmacological treatments tend to be more effective. There is also more data from the clinical review showing that drugs are effective versus placebo. And published cost effectiveness evidence also showed that drugs are cost effective versus no treatment. Therefore drugs were considered first line and are offered to all people in this age group.

Based on the cost effectiveness evidence showing that combinations are generally not cost effective, the committee did not recommend combinations for everyone (as supported by the atomoxetine model for example).The committee noted that good current practice provided group support for everyone diagnosed with ADHD that provided education about ADHD and provide -social support. Education about the condition was felt to be an important factor that was highlighted in the qualitative support review. The NICE guideline on patient experience highlights that information about your condition is important, and although it may not directly be an intervention and therefore improve health, it has other benefits that may not be captured in a measure like the QALY. The recommendation states that this could be as little as 1 to 2 sessions, and would incur significantly less cost than a full parent training programme.

It was acknowledged however as part of the review of medication (recommendation 1.10.1), that when medication has been optimised and there are still troublesome symptoms impacting on a person's everyday life the needs of the patient should be further explored.

The results of the 1 year time horizon model on CBT (and also the telephone support model which was also about individualised treatment), that used a subset of clinical data, showed combinations not to be cost effective. However the committee were concerned that the clinical review (not just the model data) was not capturing the full effects of non-pharmacological treatment. The committee agreed that the effectiveness of non-pharmacological treatments on the condition is not well captured in trials. A more global function measure would be required to capture the impact on factors like self esteem,

organisation, relationships, coping with ADHD and in general these more wider factors than just purely symptoms of hyperactivity and inattentiveness. Ideally quality of life or also perhaps the Clinical Global Impressions scales (CGI) are more global, but these were not as prominent in the review data as other outcomes that were more ADHD symptoms based.

The committee agreed it is likely there are benefits from behavioural therapies that are not being captured in the model. If t these were measurable and captured this would lead to more responders which would mean more people to accrue a higher quality of life in the model. It was the opinion of the committee therefore that particularly in adolescents, CBT in addition to medication that has been optimised would be effective at targeting those residual symptoms and this is good current practice. Hence despite the models' conclusions the committee were uncertain about the results and made a recommendation based on their clinical judgement, to consider combinations in certain circumstances.

Adults aged over 18

For adults, medication was recommended as first line. Clinical evidence from the pharmacological review found medication to be effective. Clinical opinion also agreed with this. There is limited cost effectiveness in adults regarding whether pharmacological or non-pharmacological treatment is more cost effective. Extrapolating from the atomoxetine child model – CBT is the most common form of non-pharmacological treatment provided to adults, and so taking the sensitivity analysis from the atomoxetine model where behavioural therapy was individual tells us that medication is likely to be more cost effective, because of the resource use involved in providing individual behavioural therapy. Non-pharmacological treatment was considered however in the recommendations in specific circumstances. The previous guideline model on combination treatment versus medication in adults who are stable on medication but have remaining impairment (which had a 1 year time horizon and used only two studies for effect) found individual CBT to not be cost effective. Although this model was in the right population, in terms of being in partial responders to drugs (as we are not offering combination to everyone), again the previous arguments still stand that it was considered to have limitations because the trials may not be capturing the full effect of the intervention, which would increase response rates and make the intervention more cost effective. The committee agreed that the previous guideline recommendations about considering combinations in a certain group of adults should be carried forward on clinical grounds, as cost effectiveness was uncertain at best, rather than definitive. This is good current practice and not likely to have a resource impact.

1.9.3 Other factors the committee took into account

The committee agreed that the two treatment approaches target different aspects of ADHD and should not be seen as an either or option and treatment should be focused on the person's needs. The committee noted that in an area where the evidence base is not definitive and the interventions under review have very different benefit and harm profiles, the element of patient choice and preference is of particular importance. The committee noted that people with ADHD who engage with their treatment choice are more likely to gain benefits, regardless of what that treatment choice is.

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Appendices

Appendix A: Review protocols

Table 44: Review protocol: Combined pharmacological and non-pharmacological treatment

Field	Content
Review question	What is the most clinically and cost-effective combination of pharmacological and non-pharmacological treatment for people with ADHD?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To identify the most clinically and cost-effective combination of pharmacological and/or non-pharmacological treatment for people with ADHD
Eligibility criteria – population / disease / condition / issue / domain	Children, young people and adults with ADHD. Stratified by age: • <5 years • 5 to 18 years • >18 years Note that papers will not be included if their population has been selected exclusively on the basis of response or tolerance to an intervention under investigation
Eligibility criteria – interventions	Pharmacological treatments (mixed, stimulants (including methylphenidate, dexamfetamine and lisdexamfetamine), atomoxetine) Non-pharmacological treatments (parent/family/carer training, CBT/DBT, psychoeducation, attention/memory/cognitive training, neurofeedback, relaxation techniques, organisational skills/school or workplace targeted interventions, exercise, outdoor activities Combinations of pharmacological and non-pharmacological treatments
Eligibility criteria – comparator(s) / control or reference (gold) standard	Any pharmacological treatment versus any non-pharmacological treatment Any combined treatment versus any pharmacological/non-pharmacological treatment alone Any combined treatment versus any other combined treatment Any combined treatment versus usual care
Outcomes and prioritisation	Outcomes to be extracted for end of intervention and latest follow-up if both available. Outcomes to be stratified into short term (up to 3 months follow-up) and long term (>3 months follow-up). Where multiple timepoints are reported within each definition, the longest timepoint only will be extracted. **Critical:** • Quality of life [continuous] • ADHD symptoms (total; parent/partner/carer) [continuous] • ADHD symptoms (total; teacher) [continuous]

	• ADHD symptoms (total; self-rated except for children <13) [continuous] • ADHD symptoms (total; investigator) [continuous] • ADHD symptoms (inattention; parent/partner/carer) [continuous] • ADHD symptoms (inattention; teacher) [continuous] • ADHD symptoms (inattention; self- except for children <13) [continuous] • ADHD symptoms (inattention; investigator) [continuous] • ADHD symptoms (hyperactivity/impulsivity; parent/partner/carer) [continuous] • ADHD symptoms (hyperactivity/impulsivity; teacher) [continuous] • ADHD symptoms (hyperactivity/impulsivity; self-rated except for children <13) [continuous] • ADHD symptoms (hyperactivity/impulsivity; investigator) [continuous] • Clinical Global Impressions scale – improved (much improved or very much improved) [dichotomous] **Important:** • Discontinuation due to intervention (for example perceived lack of efficacy, adverse events) [dichotomous] • Serious adverse events [dichotomous] • Behavioural measures [continuous] • Emotional dysregulation [continuous] • Academic outcomes (literacy, numeracy or combined) [continuous]
Eligibility criteria – study design	RCTs, systematic reviews of RCTs
Other inclusion exclusion criteria	Exclusions: • Crossover trials with inappropriate washout period • Pharmacological treatment received <2 weeks • Trials that only include responders to treatment under investigation • ADHD diagnosis made not using DSM-III/ICD-910 or later versions of these • Studies published after the publication of DSM-III (1978) will be included if describe their population as having a formal diagnosis of ADHD • Studies evaluating treatments for ADHD in a population of people with ASD will be included if no formal diagnosis of ADHD has been made, but evidence of moderate to severe symptoms of hyperactivity, impulsivity, and/or inattention is demonstrated according to validated symptom questionnaires)
Proposed sensitivity / subgroup analysis, or meta-regression	Previous treatment and response of population will be used for subgroup analysis in the case of heterogeneity. Studies including dietary interventions will only be included where dietary interventions are combined with pharmacological treatment and compared to an intervention other than dietary interventions alone. Dichotomous data for ADHD symptom scales other than CGI-I, will only be extracted if continuous data is not available and the definition of improved used is consistent with at least a 20% reduction in symptoms from baseline. Appraisal of methodological quality: The methodological quality of each study will be assessed using NICE checklists and GRADE.

	Stratification:
	• Age
	  ○ Pre-schoolers (under 6 years)
	  ○ Children and young people (6-17 years)
	  ○ Adults (>18 years)
	Subgroups:
	• Comorbidities:
	  ○ Intellectual disability (</>70 IQ)
	  ○ Autism spectrum (including Asperger's, PDD, NOS/atypical)
	  ○ Neurological disorder (epilepsy)
	  ○ Affective disorder (depression and anxiety all combined)
	  ○ Tic disorder and Tourette's
	  ○ Personality disorder
	  ○ Addiction
	• Age:
	  ○ Adults (18-65 years)
	  ○ Older adults (>65 years)
	• Severity
	  ○ Mild, moderate and severe
	• Population
	  ○ Previous use of interventions, degree of response
	  ○ Secure estate
	  ○ Other adults
	• Dose
	  ○ Low
	  ○ Medium
	  ○ High
	• Method of titration
	  ○ Fixed dosage
	  ○ Titrate to optimal dose
	• Diagnostic method
	  ○ DSM-III+
	  ○ ICD-10
	• Country
	  ○ UK, Europe, USA, Japan. Other countries to allocate as appropriate.
	
	For non-pharmacological interventions:
	• Mode of delivery
	• Self-help
	• Facilitated remotely (i.e. online, telephone support)
	• Face to face (1 on 1)
	• Face to face (group interventions)
	• Place of delivery
	• In educational setting (children or young adults)
	• Home setting
	• Clinic setting
	• Secure estate

Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please

	see the separate Methods report for this guideline.
Data management (software)	Databases: Medline, Embase, the Cochrane Library, Psychinfo
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library,PsycINFO Date: From October 2007 Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – from 2008 Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/cg72
Highlight if amendment to previous protocol	Not an amendment
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 of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health 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 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.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual and the methods report of this guideline
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 Centre (NGC) and chaired by Gillian Baird in line with section 3 of Developing NICE guidelines: the manual and the methods report of this guideline. Staff from NGC undertook systematic literature searches, critically appraised the evidence, conducted meta-analysis and cost-

	effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 45: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocols in appendix A above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B. For questions being updated, the search will be run from December 2007, which was the cut-off date for the searches conducted for NICE guideline CG72
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2001 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[46] Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion

Review question	All questions – health economic evidence
	The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix I. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. Economic evaluations that are based on studies excluded from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, Oct 2014, updated 2017. https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 46: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 October 2007 – 28 April 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	01 October 2007 – 28 April 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews 2007 to 2017 Issue 4 of 12 CENTRAL 2007 to 2017 Issue 3 of 12 DARE and NHSEED 2007 to 2015 Issue 1 of 4 HTA 2007 to 2017 Issue 1 of 4	None
PsycINFO (ProQuest)	01 October 2007 – 28 April 2017	Exclusions Randomised controlled trials Systematic review studies

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(ADHD or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	exp Child Development Disorders, Pervasive/
10.	(autistic or autism or asperger*).ti,ab.
11.	pervasive developmental disorder*.ti,ab.

12.	(asd or pdd or pdd-nos).ti,ab.
13.	or/9-12
14.	hyperkinesis/
15.	(hyperactiv* or inattent* or hyperkin* or hyper-kin*).ti,ab.
16.	14 or 15
17.	13 and 16
18.	8 or 17
19.	limit 18 to English language
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	Animals, Laboratory/
33.	exp animal experiment/
34.	exp animal model/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ab.
42.	placebo.ab.
43.	drug therapy.fs.
44.	randomly.ab.
45.	trial.ab.
46.	groups.ab.
47.	or/39-46
48.	Clinical Trials as topic.sh.
49.	trial.ti.
50.	or/39-42,44,48-49
51.	Meta-Analysis/
52.	Meta-Analysis as Topic/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(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.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	38 and (50 or 61)

Embase (Ovid) search terms

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(ADHD or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	exp autism/
10.	(autistic or autism or asperger*).ti,ab.
11.	pervasive developmental disorder*.ti,ab.
12.	(asd or pdd or pdd-nos).ti,ab.
13.	or/9-12
14.	hyperactivity/
15.	hyperkinesia/
16.	(hyperactiv* or inattent* or hyperkin* or hyper-kin*).ti,ab.
17.	or/14-16
18.	13 and 17
19.	8 or 18
20.	limit 19 to English language
21.	letter.pt. or letter/
22.	note.pt.
23.	editorial.pt.
24.	case report/ or case study/
25.	(letter or comment*).ti.
26.	or/21-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animal/ not human/
30.	nonhuman/
31.	exp Animal Experiment/
32.	exp Experimental Animal/

33.	animal model/
34.	exp Rodent/
35.	(rat or rats or mouse or mice).ti.
36.	or/28-35
37.	20 not 36
38.	random*.ti,ab.
39.	factorial*.ti,ab.
40.	(crossover* or cross over*).ti,ab.
41.	((doubl* or singl*) adj blind*).ti,ab.
42.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
43.	crossover procedure/
44.	single blind procedure/
45.	randomized controlled trial/
46.	double blind procedure/
47.	or/38-46
48.	systematic review/
49.	meta-analysis/
50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(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.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	37 and (47 or 58)

Cochrane Library (Wiley) search terms

#1.	[mh ^"attention deficit and disruptive behavior disorders"]
#2.	[mh ^"attention deficit disorder with hyperactivity"]
#3.	((attenti* or disrupt*) near/3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)):ti
#4.	((attenti* or disrupt*) near/3 disorder*):ab
#5.	(ADHD or addh or ad next hd or ad-hd):ti,ab
#6.	(attenti* near/3 deficit*):ti,ab
#7.	(((hyperkin* or (hyper near/1 kin*)) near/1 (syndrome* or disorder*)) or hkd):ti,ab
#8.	(minimal near/1 brain near/2 (dysfunct* or disorder*)):ti,ab
#9.	(or #1-#8)
#10.	[mh "Child Development Disorders, Pervasive"]
#11.	(autistic or autism or asperger*):ti,ab
#12.	(pervasive next developmental next disorder*):ti,ab

#13.	(asd or pdd or pdd-nos):ti,ab
#14.	(or #10-#13)
#15.	[mh ^hyperkinesis]
#16.	(hyperactiv* or inattent* or hyperkin* or hyper-kin*):ti,ab
#17.	#15 or #16
#18.	#14 and #17

PsycINFO (ProQuest) search terms

1.	(SU.EXACT.EXPLODE("Attention Deficit Disorder") OR TI((attenti* OR disrupt*) NEAR/3 (adolescent* OR adult* OR behav* OR child* OR class OR classes OR classroom* OR condition* OR difficult* OR disorder* OR learn* OR people OR person* OR poor OR problem* OR process* OR youngster*)) OR AB((attenti* OR disrupt*) NEAR/3 disorder*) OR TI,AB(ADHD OR addh OR ad-hd OR ad??hd) OR TI,AB(attenti* NEAR/3 deficit*) OR TI,AB(((hyperkin* OR (hyper-kin*)) NEAR/1 (syndrome* OR disorder*)) OR hkd) OR TI,AB(minimal NEAR/1 brain NEAR/2 (dysfunct* OR disorder*))) OR ((SU.EXACT.EXPLODE("Autism Spectrum Disorders") or TI,AB(autistic or autism or asperger*) or TI,AB(pervasive-developmental-disorder*) or TI,AB(asd or pdd or pdd-nos)) AND (SU.EXACT("Hyperkinesis") or TI,AB(hyperactiv* or inattent* or hyperkin* or hyper-kin*)))
2.	(su.exact.explode("clinical trials") OR ti,ab((clinical OR control*) NEAR/3 trial*) OR ti,ab((single* OR double* OR treble* OR triple*) NEAR/5 (blind* OR mask*)) OR ti,ab(volunteer* OR control-group OR controls) OR su.exact("placebo") OR ti,ab(placebo*))
3.	((SU.EXACT("Literature Review") or RTYPE(review) or ti(review) or me(literature review)) AND (ti,ab(systematic or evidence or methodol* or quantitative*))) or (SU.EXACT("Meta Analysis") or ti,ab(meta-analys* or metanalys* or metaanalys* or meta analys*) or ti,ab((systematic or evidence* or methodol* or quantitative*) near/3 (review* or overview*)) or ti,ab((pool* or combined or combining) near/2 (data or trials or studies or results)) or RTYPE(systematic or meta*) or ME(meta analysis or systematic review))
4.	1 AND (2 OR 3)
5.	Limit to English
6.	NOT (Dissertations & Theses AND Books)

B.2 Health Economics literature search strategies

B.2.1 Health economics search strategy

Health economic evidence was identified by conducting a broad search relating to ADHD population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 47: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 28 April 2017	Exclusions Health economics
Embase	2014 – 28 April 2017	Exclusions Health economics

Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - 2008 – 28 April 2017 NHSEED - 2008 to March 2015	None

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(ADHD or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/
38.	budget*.ti,ab.

39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

Embase (Ovid) search terms

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(ADHD or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/

22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Attention Deficit and Disruptive Behavior Disorders
#2.	MeSH DESCRIPTOR Attention Deficit Disorder with Hyperactivity
#3.	(((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*))):TI
#4.	(((attenti* or disrupt*) adj3 disorder*))
#5.	((ADHD or addh or ad hd or ad??hd))
#6.	((attenti* adj3 deficit*))
#7.	((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd))

#8.	((minimal brain adj2 (dysfunct* or disorder*)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(#9) IN NHSEED, HTA

B.2.2 Quality of Life search strategy

Quality of life evidence was identified by conducting a broad search relating to ADHD population in Medline and Embase.

Table 48: Database date parameters and filters used

Database	Dates searched	Search filters used
Medline	2008 – 28 September 2015	Exclusions Quality of life
Embase	2008 – 28 September 2015	Exclusions Quality of life

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(ADHD or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/

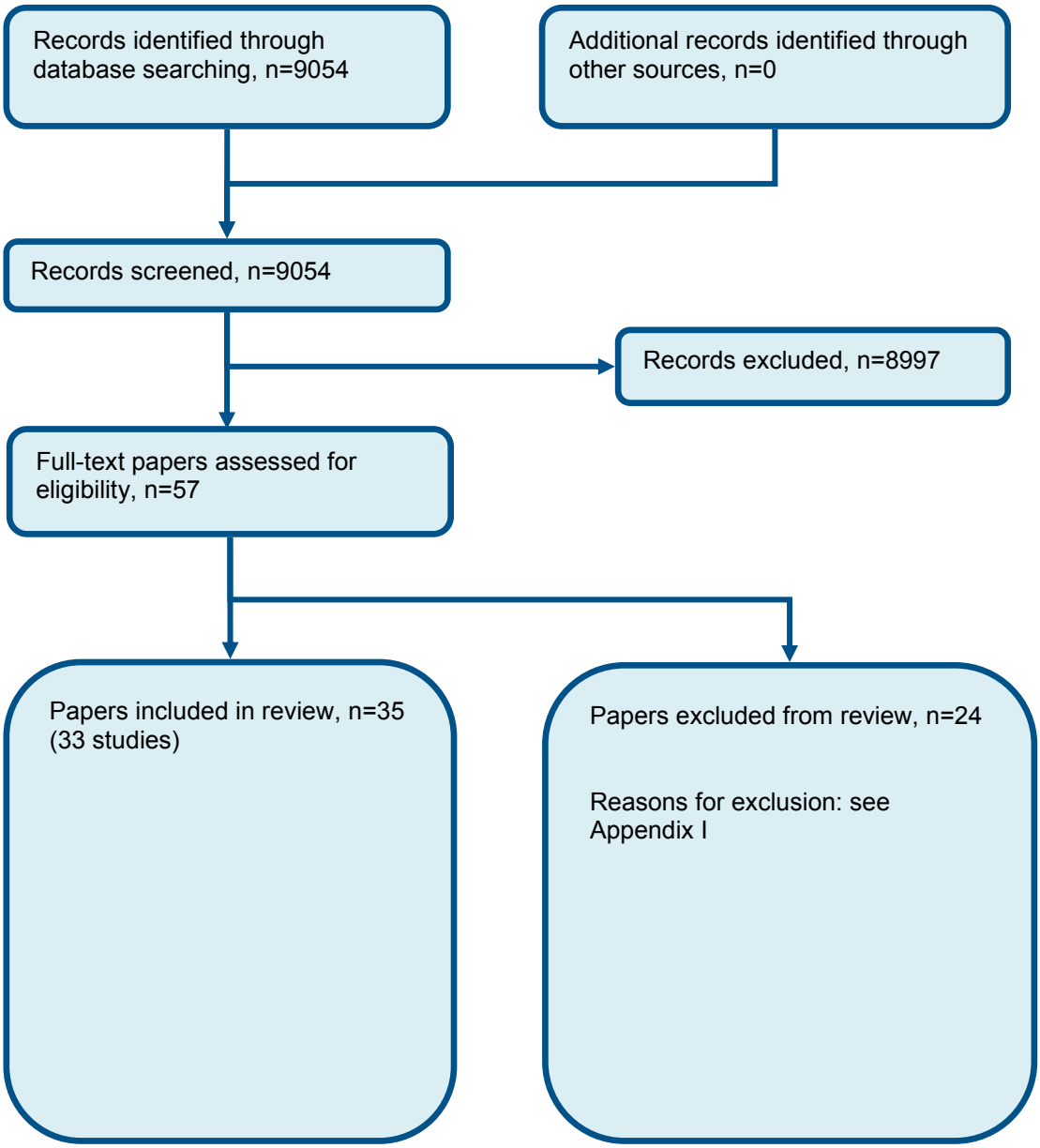
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	quality-adjusted life years/
30.	sickness impact profile/
31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
48.	or/29-47
49.	28 and 48

Embase (Ovid) search terms

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(ADHD or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.

17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	quality adjusted life year/
28.	"quality of life index"/
29.	short form 12/ or short form 20/ or short form 36/ or short form 8/
30.	sickness impact profile/
31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
48.	or/27-47
49.	26 and 48

Appendix C: Clinical evidence selection



Appendix D: Clinical evidence tables

Study	Abikoff 2004[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=103)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis:
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	7 to 9.9 years old, met diagnostic criteria for ADHD, responded to 5 week open label trial of methylphenidate
Exclusion criteria	Conduct disorder, learning disorder
Age, gender and ethnicity	Age - Mean (SD): 8.2 (0.8). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 3. Previous treatment: Previously on drugs, responsive
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Pharma + non-pharma - Stimulants + carer/family +/- teacher training. Methylphenidate (for 2 years) + multimodal psychosocial treatment (for 1 year, including parent training and counselling, academic assistance, psychotherapy and social skills training). Duration 2 years. Concurrent medication/care: Nil else (n=35) Intervention 2: Pharma + non-pharma - Stimulants + coaching/mentoring/psychoeducation/counselling. Methylphenidate (for 2 years) + attention control treatment (for 1 year, counselling excluding the specific aspects of the psychosocial intervention). Duration 2 years. Concurrent medication/care: Nil else (n=34) Intervention 3: CNS stimulants - Methylphenidate. 2 years of methylphenidate. Duration 2 years . Concurrent medication/care: Nil else
Funding	Principal author funded by industry

Study	Abikoff 2004[3]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + PT/FT versus STIMULANTS + NSST

Protocol outcome 1: ADHD symptoms - Hyperactivity at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, parent rated, CTRS, 0-3, higher is worse at 12 months PT; Group 1: mean 1.2 (SD 0.6); n=34, Group 2: mean 1 (SD 0.6); n=35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, parent rated, CTRS, 0-3, higher is worse at 12 months FU; Group 1: mean 0.9 (SD 0.5); n=34, Group 2: mean 0.8 (SD 0.4); n=35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, teacher rated, CTRS, 0-3, higher is worse at 12 months PT; Group 1: mean 0.9 (SD 0.8); n=34, Group 2: mean 0.9 (SD 0.7); n=35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, teacher rated, CTRS, 0-3, higher is worse at 12 months FU; Group 1: mean 1 (SD 0.7); n=34, Group 2: mean 0.7 (SD 0.4); n=35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + PT/FT versus METHYLPHENIDATE

Protocol outcome 1: ADHD symptoms - Hyperactivity at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, parent rated, CTRS, 0-3, higher is worse at 12 months PT; Group 1: mean 1.2 (SD 0.6); n=34, Group 2: mean 1.1 (SD 0.6); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, parent rated, CTRS, 0-3, higher is worse at 12 months FU; Group 1: mean 0.9 (SD 0.5); n=34, Group 2: mean 1 (SD 0.6); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, teacher rated, CTRS, 0-3, higher is worse at 12 months FU; Group 1: mean 1 (SD 0.7); n=34, Group 2: mean 1.1 (SD 0.8); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Study	Abikoff 2004[3]
Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, teacher rated, CTRS, 0-3, higher is worse at 12 months PT; Group 1: mean 0.9 (SD 0.8); n=34, Group 2: mean 1.2 (SD 0.9); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + NSST versus METHYLPHENIDATE Protocol outcome 1: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, parent rated, CTRS, 0-3, higher is worse at 12 months PT; Group 1: mean 1 (SD 0.6); n=35, Group 2: mean 1.1 (SD 0.6); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, teacher rated, CTRS, 0-3, higher is worse at 12 months PT; Group 1: mean 0.9 (SD 0.7); n=35, Group 2: mean 1.2 (SD 0.9); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, parent rated, CTRS, 0-3, higher is worse at 12 months FU; Group 1: mean 0.8 (SD 0.4); n=35, Group 2: mean 1 (SD 0.6); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, teacher rated, CTRS, 0-3, higher is worse at 12 months FU; Group 1: mean 0.7 (SD 0.4); n=35, Group 2: mean 1.1 (SD 0.8); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Dose 2016[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=103)
Countries and setting	Conducted in Germany; Setting: Germany
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6 to 12, using MPH at a stable dose for 2 months, still showing functional impairment, not already in possible psychotherapy
Exclusion criteria	Nil extra
Recruitment/selection of patients	Study information sent to ~3,600 child psychiatrists and promoted online
Age, gender and ethnicity	Age - Range: Child aged 6 to 12. Gender (M:F): Not stated. Ethnicity:
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 3. Previous treatment: Previously on drugs, not responsive
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Pharma + non-pharma - Stimulants + carer/family +/- teacher training. PT involving booklets mailed to parents every 2 weeks with 10 telephone consultations with "counsellors" of 30 minutes over first 6 months, 4 booster telephone consultations over second 6 months. Continued on previous methylphenidate (some switched or altered doses). Duration 12 months. Concurrent medication/care: Usual care (n=52) Intervention 2: CNS stimulants - Methylphenidate. Continued on previous methylphenidate and nil else. Duration 12 months. Concurrent medication/care: Usual care
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH + PT/FT versus MPH Protocol outcome 1: ADHD symptoms (total) at >3 months	

Study	Dose 2016[9]
- Actual outcome for Children and young people 5 to 18: FBB-ADHS, total, parent rated at 12 months PT (end of booster); Group 1: mean 1.29 (SD 0.62); n=51, Group 2: mean 1.5 (SD 0.63); n=52; FBB-ADHS 0-3 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: ADHD symptoms - Inattention at >3 months - Actual outcome for Children and young people 5 to 18: FBB-ADHS, inattention, parent rated at 12 months PT (end of booster); Group 1: mean 1.38 (SD 0.62); n=51, Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: FBB-ADHS, H/I, parent rated at 12 months PT (end of booster); Group 1: mean 1.22 (SD 0.69); n=51, Group 2: mean 1.36 (SD 0.8); n=52 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Behaviour/function at >3 months - Actual outcome for Children and young people 5 to 18: Functional, WFIRS-P total, parent rated at 12 months PT (end of booster); Group 1: mean 0.86 (SD 0.45); n=51, Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Hyperactivity at <3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Duric 2014[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=130)
Countries and setting	Conducted in Norway; Setting: outpatient
Line of therapy	1st line

Study	Duric 2014[10]
Duration of study	Intervention time: not reported (probably ca 10 weeks. "30 NF treatments for the duration of the study. Three sessions per week were conducted"
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: assessment included a clinical psychiatric interview and observations to assess ADHD and other appropriate diagnoses. Questionnaires regarding ADHD were filled out by the children, parents, and teachers of the children. A medical examination was done to exclude somatic conditions causing ADHD symptoms. A child psychiatrist evaluated the assessments and categorized the children as having ADHD or a non-ADHD condition according to ICD-10 diagnostic criteria
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable:
Inclusion criteria	Children and adolescents with ADHD (aged under 18 years) who were diagnosed with ADHD
Exclusion criteria	no information
Recruitment/selection of patients	Children and adolescents with ADHD (aged under 18 years) who were diagnosed with ADHD at the Child and Adolescent Mental Health Clinic, from 2007 to 2009, were invited to participate
Age, gender and ethnicity	Age - Mean (range): 11.5 [6-17]. Gender (M:F): 106/24. Ethnicity: unknown
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (children and adolescents (aged under 18). 3. Previous treatment: Not stated / Unclear
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: CNS stimulants - Methylphenidate. Subjects were administered MPH twice per day, at the recommended dose of1 mg/kg, with total daily dosages ranging from 20 to 60 mg. Duration ca 10 weeks. Concurrent medication/care: - Comments: no information about the duration of the treatment / study duration. Neurofeedback included 30 treatments and 3 session per week, so probably 10 weeks duration. unclear how many children were randomised to each group; 130 children were randomised; 91 completed treatment; 80 children agreed to fill out questionnaires. Numbers per intervention were only reported for this subgroup of 80 children (n=28) Intervention 2: Neurofeedback. Each participant was provided with 30 NF treatments for the duration of the study. Three sessions per week were conducted. The duration of each session was 45 minutes where each session started with 5 minutes of relaxation using alpha enhancement feedback, followed by two training sessions of twenty minutes each. The NF training was based on the standard theta/beta protocol in Cz for ADHD treatments from Lubar (Association for Applied Psychophysiology and Biofeedback).39,40 In this protocol beta activity (16–20 Hz) is enhanced and theta (4–7 Hz) is suppressed. The goal was to

Study	Duric 2014[10]
	decrease theta activity by inhibiting high amplitude theta activity and by simultaneously rewarding high amplitude beta activity. Successful treatment was defined as a significant increase in beta activity, and a decrease in theta and EMG activities. Rewards were given if participants could keep theta levels below threshold 70% of the treatment time and keep beta levels above threshold 20% of the time. Depending on the participant's performance these reward thresholds were manually adjusted by the therapist. In addition, the therapist verbally reinforced the participant's performance and helped with progress. Duration ca 10 weeks. Concurrent medication/care: unknown Comments: no information about the duration of the treatment / study duration unclear how many children were randomised to each group; 130 children were randomised; 91 completed treatment; 80 children agreed to fill out questionnaires. Numbers per intervention were only reported for this subgroup of 80 children (n=25) Intervention 3: Pharma + non-pharma - Other. Subjects were administered MPH twice per day, at the recommended dose of1 mg/kg, with total daily dosages ranging from 20 to 60 mg. Each participant was provided with 30 NF treatments for the duration of the study. Three sessions per week were conducted. The duration of each session was 45 minutes where each session started with 5 minutes of relaxation using alpha enhancement feedback, followed by two training sessions of twenty minutes each. The NF training was based on the standard theta/beta protocol in Cz for ADHD treatments from Lubar (Association for Applied Psychophysiology and Biofeedback).39,40 In this protocol beta activity (16–20 Hz) is enhanced and theta (4–7 Hz) is suppressed. The goal was to decrease theta activity by inhibiting high amplitude theta activity and by simultaneously rewarding high amplitude beta activity. Successful treatment was defined as a significant increase in beta activity, and a decrease in theta and EMG activities. Rewards were given if participants could keep theta levels below threshold 70% of the treatment time and keep beta levels above threshold 20% of the time. Depending on the participant's performance these reward thresholds were manually adjusted by the therapist. In addition, the therapist verbally reinforced the participant's performance and helped with progress. Duration ca 10 weeks. Concurrent medication/care: - Comments: no information about the duration of the treatment / study duration unclear how many children were randomised to each group; 130 children were randomised; 91 completed treatment; 80 children agreed to fill out questionnaires. numbers per intervention were only reported for this subgroup of 80 children
Funding	No funding (The authors declare that there are no financial or non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) in relation to this manuscript.)

Study	Duric 2014[10]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROFEEDBACK versus METHYLPHENIDATE Protocol outcome 1: ADHD symptoms - Inattention at <3 months - Actual outcome: ADHD symptoms, attention (SRQ) at post treatment; Group 1: mean 6.4 (SD 2.1); n=25, Group 2: mean 6.8 (SD 2.1); n=27; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale 1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given; Group 2 Number missing: Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. Protocol outcome 2: ADHD symptoms - Hyperactivity at <3 months - Actual outcome: ADHD symptoms, hyperactivity (SRQ) at post treatment; Group 1: mean 5.6 (SD 2.8); n=25, Group 2: mean 6.4 (SD 2.7); n=27; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale 1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. Protocol outcome 3: Academic outcomes at <3 months - Actual outcome: school performance (SRQ) at post treatment; Group 1: mean 7.2 (SD 2.5); n=24, Group 2: mean 6.9 (SD 2.4); n=27; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical	

Study	Duric 2014[10]
reasons. during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE + NEUROFEEDBACK versus METHYLPHENIDATE Protocol outcome 1: ADHD symptoms - Inattention at <3 months - Actual outcome: ADHD symptoms attention (SRQ) at post treatment; Group 1: mean 6.3 (SD 2.1); n=25, Group 2: mean 6.8 (SD 2.1); n=27; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale 1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. Protocol outcome 2: ADHD symptoms - Hyperactivity at <3 months - Actual outcome: ADHD symptoms, hyperactivity (SRQ) at post treatment; Group 1: mean 7.1 (SD 2.3); n=25, Group 2: mean 6.4 (SD 2.7); n=27; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD(inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale1-10. Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 3: Academic outcomes at <3 months - Actual outcome: school performance (SRQ) at post treatment; Group 1: mean 6.3 (SD 2.7); n=22, Group 2: mean 6.9 (SD 2.4); n=27; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD(inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons.

Study	Duric 2014[10]
during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE + NEUROFEEDBACK versus NEUROFEEDBACK Protocol outcome 1: ADHD symptoms - Inattention at <3 months - Actual outcome: ADHD symptoms attention (SRQ) at post treatment; Group 1: mean 6.3 (SD 2.1); n=25, Group 2: mean 6.4 (SD 2.1); n=25; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale 1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. Protocol outcome 2: ADHD symptoms - Hyperactivity at <3 months - Actual outcome: ADHD symptoms, hyperactivity (SRQ) at post treatment; Group 1: mean 7.1 (SD 2.3); n=25, Group 2: mean 5.6 (SD 2.8); n=25; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale1-10. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given. Protocol outcome 3: Academic outcomes at <3 months - Actual outcome: school performance (SRQ) at post treatment; Group 1: mean 6.3 (SD 2.7); n=22, Group 2: mean 7.2 (SD 2.5); n=24; self-reporting questionnaire SRQ 1-10 Top=High is poor outcome; Comments: developed by researchers with questions derived from other questionnaires (self-rating scale of self-regulatory function, piers-Harris Children self-concept scale). SRQ consists of 5 items, 2 concerning ADHD (inattention, hyperactivity) and 3 regarding school performance (mathematics, reading, writing skills). children were asked how they rate themselves on scale 1-10.

Study	Duric 2014[10]
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: baseline score hyperactivity (scale 1-10); methylphenidate: mean 5.1, methylphenidate and neurofeedback mean 6.0, neurofeedback: mean 4.2; Group 1 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given.; Group 2 Number missing: , Reason: drop out before start treatment, after randomisation: did not agree to fill out questionnaires, lack parental interest, loss of motivation, other practical reasons. during treatment dropped out with no reason given.	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months

Study	Duric 2017[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=130)
Countries and setting	Conducted in Norway; Setting: The child and adolescent mental health clinic (CAMHC) at Haugesund Hospital in Norway.
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months and 6 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	All children who met the following criteria were invited to participate: symptomatology consistent with DSM-IV criteria for the diagnosis of ADHD; age 6-18 years; and cognitive function above an intelligence quotients of 70. The children were evaluated using the Wechsler Intelligence Scale for Children (WISC-IV)
Exclusion criteria	Children who met the following criteria were excluded from the study: involvement in another intervention group, including CBT and Stop Now and Plan (SNAP); the presence of co-morbid disorders other than ODD or anxiety disorder; and the presence of a neurological and/or cardiovascular condition.

Study	Duric 2017[11]
Age, gender and ethnicity	Age - Mean (SD): 11.2 (2.8). Gender (M:F): 72 boys, 19 girls (based on 91 participants). Ethnicity: Not stated.
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (Aged 6-18). 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Neurofeedback. Neurofeedback - Unipolars placed on the patients scalp to process signals as brainwaves or computer frequencies, while measuring brain activity. Brain activities then shown to the subject through a video game or a film, so they could attempt to change their activity level. The child was allowed to play the video game to produce the desired brainwaves, which helps shape the brainwaves to a more regulated performance. NF conducted using Infinity software and equipment. All participants underwent NF treatment three times a week, with a total of 30 sessions. . Duration 3 months. Concurrent medication/care: All three intervention groups received treatment for 3 months administrated of the child and adolescent psychiatrist. (n=44) Intervention 2: CNS stimulants - Methylphenidate. Methylphenidate - Subjects treated with MPH at a dosage of 1mg/kg/day in the form of long-acting MPH capsules. The total dose of MPH was between 2-60mg. Compliance and side-effects were recorded. Duration 3 months. Concurrent medication/care: All three intervention groups received treatment for 3 months administrated of the child and adolescent psychiatrist. (n=44) Intervention 3: Pharma + non-pharma - Other. Combination of methylphenidate and NF - Methylphenidate - Subjects treated with MPH at a dosage of 1mg/kg/day in the form of long-acting MPH capsules. The total dose of MPH was between 2-60mg. Compliance and side-effects were recorded. Neurofeedback - Unipolars placed on the patients scalp to process signals as brainwaves or computer frequencies, while measuring brain activity. Brain activities then shown to the subject through a video game or a film, so they could attempt to change their activity level. The child was allowed to play the video game to produce the desired brainwaves, which helps shape the brainwaves to a more regulated performance. NF conducted using Infinity software and equipment. All participants underwent NF treatment three times a week, with a total of 30 sessions. . Duration 3 months. Concurrent medication/care: All three intervention groups received treatment for 3 months administrated of the child and adolescent psychiatrist.
Funding	Other (Thanks to the Child and Adolescent Psychiatry Department of Helse Fonna Hospital Haugesund, Helse Fonna Trust Haugesund, Norway for its support in completing this study.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROFEEDBACK versus METHYLPHENIDATE

Study	Duric 2017[11]
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parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms total 3 months PT - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Parent rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 14, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 13, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 2: ADHD symptoms (total) at >3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms total 6 months FU - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Teacher rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms total 6 months FU - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Parent rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 3: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention 3 months PT - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Teacher rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 14, Reason: MPH+NF - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention 3 months PT - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Parent rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 14, Reason: MPH+NF - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention 3 months PT - measured with self report questionnaire (SRQ). Self rated. at 3 months PT;

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Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 13, Reason: MPH+NF - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 4: ADHD symptoms - Inattention at >3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention 6 months FU - measured with Barkley's defiant children: a clinicians manual for assessment and parent training. Teacher rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention 6 months FU - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Parent rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention 6 months FU - measured with self report questionnaire (SRQ). Self rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 5: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity 3 months PT - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Teacher rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 14, Reason: MPH+NF - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity 3 months PT - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Parent rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 14, Reason: MPH+NF - dropped out due to either	

Study	Duric 2017[11]
	parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity 3 months PT - measured with self report questionnaire (SRQ). Self rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 14, Reason: MPH+NF - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 6: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity 6 months FU - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Teacher rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 18, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 16, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity 6 months FU - measured with Barkleys defiant children: a clinicians manual for assessment and parent training. Parent rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity 6 months FU - measured with self report questionnaire (SRQ). Self rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 7: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: Academic outcomes 3 months PT - measured with self report questionnaire (SRQ). Self rated. at 3 months PT; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 13, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 14, Reason: MPH+NF - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. Protocol outcome 8: Academic outcomes at >3 months

Study	Duric 2017[11]
- Actual outcome for Children and young people 5 to 18: Academic outcomes 6 months FU - measured with self report questionnaire (SRQ). Self rated. at 6 months FU; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: -- ; Group 1 Number missing: 16, Reason: MPH - dropped out due to either parental or participants' lack of interest and motivation or other practical reasons. ; Group 2 Number missing: 15, Reason: MPH+NF- dropped out due to either parental or participants' lack of interest and motivation or other practical reasons.	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months

Study	Emilsson 2011[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=54)
Countries and setting	Conducted in Iceland; Setting: Outpatient clinic.
Line of therapy	1st line
Duration of study	Intervention + follow up: 21 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) ADHD section and has been modified for adults and translated into Icelandic.
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients required to have a clinical diagnosis of ADHD and to be stable on prescribed ADHD medication for at least a month, i.e. stimulants, atomoxetine or bupropion. The participants were told to try and keep dosages unchanged during the whole study.
Exclusion criteria	Exclusion criteria included patients with severe mental illness, active drug abuse, verbal IQ estimated from clinical records to be below 85, no valid ADHD diagnosis or not prescribed/taking ADHD medication.
Recruitment/selection of patients	Referred to an outpatient rehabilitation clinic within the Mental Health Services at the Landspitali - The National University Hospital of Iceland or self-referred from an advertisement to members of the Icelandic ADHD association, a national support organization.
Age, gender and ethnicity	Age - Mean (SD): 33.88 (11.47). Gender (M:F): 20 men : 34 women. Ethnicity: Not reported

Study	Emilsson 2011[12]
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (K-SADS ADHD (Mean (SD)): CBT= 40.02 (5.35) ; TAU= 38.16 (8.14)). 2. Age: Adults 18-65 (Mean age of 33.88). 3. Previous treatment: Not applicable
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Pharma + non-pharma - Mixed medication + CBT. R&R2ADHDis a 15 session manualised CBT intervention programme that was developed in 2007for youths and adults with ADHD and antisocial behaviour. It is a revised edition of the 35-session Reasoning &Rehabilitation programme that was originally developed as a prosocial competence training programme for use in correctional facilities and its feasibility and effectiveness are well supported in this population [36,37]. R&R2ADHD is a structured, manualised programme that aims to decrease impairment of core ADHD symptoms and improve social, problem solving, and organizational skills. It consists of five treatment modules (1) neurocognitive, e.g. learning strategies to improve attentional control, memory, impulse control and planning, (2) problem solving, e.g. developing skilled thinking, problem identification, consequential thinking, managing conflict and making choices,(3) emotional control, e.g. managing feelings of anger and anxiety, (4)pro-social skills, e.g. recognition of the thoughts and feeling of others, empathy, negotiation skills and conflict resolution, and (5)critical reasoning, e.g. evaluating options and effective behavioural skills. The programme integrates group and individual treatment, the latter being achieved by group facilitators training 'coaches' who meet with the participant between sessions. The coaching role aims to support participants to transfer skills learned in the group into their daily lives. In the present study the coach role was fulfilled by psychology undergraduates. This programme was delivered according to a manual and the coaches also received directions through training and written guidelines. All R&R2ADHD facilitators had extensive experience in CBT and received training in delivering the programme. Duration 8 weeks. Concurrent medication/care: All participants were on medication to treat ADHD and were asked not to change their intake during the trial. (n=27) Intervention 2: Mixed medication - Non-specific medication. At baseline, 42 were receiving methylphenidate, 11 atomoxetine, 5 bupropion and 1 amphetamine sulphate. Duration 8 weeks. Concurrent medication/care: All participants were on medication to treat ADHD and were asked not to change their intake during the trial.
Funding	Other (RANNIS the Icelandic Centre for Research (Nr. 080443022), the Landspital Science Fund, and Janssen-Cilag, Iceland.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDICATION + CBT versus MEDICATION + USUAL CARE

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Adults over 18: Barkley ADHD Current Symptoms Scale - total - 8 weeks PT at 8 weeks PT; Group 1: mean 17.22 (SD 7.62); n=18, Group 2: mean 23.47 (SD 8.8); n=17; Barkley ADHD Current Symptoms Scale (BCS) 0-54 Top=High is poor outcome; Comments: Self-reported

Study	Emilsson 2011[12]
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 2: ADHD symptoms (total) at >3 months - Actual outcome for Adults over 18: Barkley ADHD Current Symptoms Scale - total - 3 months FU at 3 months FU; Group 1: mean 15.7 (SD 8.74); n=15, Group 2: mean 25 (SD 8.54); n=17; Barkley ADHD Current Symptoms Scale (BCS) 0-54 Top=High is poor outcome; Comments: Self-reported Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 3: ADHD symptoms - Inattention at <3 months - Actual outcome for Adults over 18: Barkley ADHD Current Symptoms Scale - inattention - 8 weeks PT at 8 weeks PT; Group 1: mean 10.17 (SD 4.44); n=18, Group 2: mean 14.71 (SD 5.19); n=17; Barkley ADHD Current Symptoms Scale (BCS) 0-27 Top=High is poor outcome; Comments: Self-reported Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements.; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 4: ADHD symptoms - Inattention at >3 months - Actual outcome for Adults over 18: Barkley ADHD Current Symptoms Scale - inattention - 3 months FU at 3 months FU; Group 1: mean 9.76 (SD 5.62); n=15, Group 2: mean 16.24 (SD 5.66); n=17; Barkley ADHD Current Symptoms Scale (BCS) 0-27 Top=High is poor outcome; Comments: Self-reported Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements.; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 5: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: Barkley ADHD Current Symptoms Scale - hyperactivity - 8 weeks PT at 8 weeks PT; Group 1: mean 7.06 (SD 4.41); n=18, Group 2: mean 8.76 (SD 6.22); n=17; Barkley ADHD Current Symptoms Scale (BCS) 0-27 Top=High is poor outcome; Comments: Self-reported. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,	

Study	Emilsson 2011[12]
Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements.; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 6: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Adults over 18: Barkley ADHD Current Symptoms Scale - hyperactivity - 3 months FU at 3 months FU; Group 1: mean 5.94 (SD 4.12); n=15, Group 2: mean 8.76 (SD 5.43); n=17; Barkley ADHD Current Symptoms Scale (BCS) 0-27 Top=High is poor outcome; Comments: Self-reported Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements.; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 7: CGI-I at <3 months - Actual outcome for Adults over 18: The Clinical Global Impressions Scale (CGI) - 8 weeks PT at 8 weeks PT; Group 1: mean 3.18 (SD 1.07); n=17, Group 2: mean 3.88 (SD 0.7); n=17; The Clinical Global Impressions Scale (CGI) 1-7 Top=High is poor outcome; Comments: Clinician rated Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements.; Group 2 Number missing: 10, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy. Protocol outcome 8: CGI-I at >3 months - Actual outcome for Adults over 18: The Clinical Global Impressions Scale (CGI) - 3 months FU at 3 months FU; Group 1: mean 3 (SD 0.76); n=8, Group 2: mean 4.08 (SD 0.86); n=13; The Clinical Global Impressions Scale (CGI) 1-7 Top=High is poor outcome; Comments: Clinician rated Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: Without explanation, moving out of the area, illness in the family and stop medication due to pregnancy. Not filling in the measurements.; Group 2 Number missing: 14, Reason: Four dropped out during the treatment phase without explanation, one due to moving out of the area, one due to illness in the family and one had to stop medication due to pregnancy.	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Estrada 2013[13]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in Spain; Setting: Clinic
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Conners' Adult ADHD Diagnostic Interview for DSM-IV
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with ADHD who were in pharmacological treatment but still reporting clinically significant symptoms. They had to fulfill the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), diagnostic criteria for ADHD, to be older than 18 years, to have stable medication prescribed for 2 months, and to have obtained a minimum score of 24 on the ADHD Rating Scale (ADHD-RS) and a minimum score of 4 on the Clinical Global Impression Severity Scale (CGI-S). Participants who had a history of psychiatric comorbidity but had stabilized symptoms at the moment of the study were also included.
Exclusion criteria	History of substance abuse in the past 6 months or current comorbidity of other axis I or II disorders of DSM-IV (APA, 1994). Patients with significant symptoms of depression and anxiety measured by the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI), but who did not comply with the criteria for anxiety and affective disorders as measured by the Structured Clinical Interview for DSM-IVAxis I Disorders (SCID-I), were included in this study.
Recruitment/selection of patients	Adult ADHD Program at the Hospital Vall d'Hebron in Barcelona
Age, gender and ethnicity	Age - Mean (SD): 39.47 (7.68). Gender (M:F): 15/17. Ethnicity:
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (ADHD-RS (mean (SD)) - PE= 30.53 (10.26); CBT= 31.47 (7.75)). 2. Age: Adults 18-65 (18 years or older). 3. Previous treatment: Previously on drugs, mixed (Patients with partial response to the pharmacological treatment were referred to this study by clinicians of the team.).
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Pharma + non-pharma - Mixed medication + coaching/mentoring/psychoeducation/counselling. The focus of the program was to provide education and information about ADHD. The contents of the psychoeducation program were basically informative:

Study	Estrada 2013[13]
	symptoms recognition (diagnosis and characteristics of ADHD, positive and negative symptoms), disorder comprehension (myths and realities in ADHD), causal and triggering factors (ADHD causes), information about pharmacological and psychological treatment, relaxation, providing information on cognitive aspects (cognitive model of ADHD), and information on behavioural factors of ADHD (attention deficits, difficulties in problem solving and planning). The information given was focused on difficulties in ADHD but not on the solutions of these difficulties. The program also included a psychoeducation session with one family member. No practice skills were included in the program. Neither homework tasks nor material for the participants was given. During the sessions, the psychologists always referred to psychoeducational information and avoided the use of the treatment components included in the cognitive behavioural program. Thus, they directed the content to understanding of the problems associated with ADHD. . Duration 12 weeks. Concurrent medication/care: At the start of treatment everyone used medication (metilfenidate N=13, Atomoxetine N=3, Bupropion N=1) (n=15) Intervention 2: Pharma + non-pharma - Mixed medication + CBT. The CBT-program focused on coping skills training: behavioural interventions (distractions delaying, planification skills, and procrastination management) and cognitive techniques (problem solving, functional analysis, thoughts identification, and cognitive restructuring). It also included limited psychoeducation (one session). In contrast with the psychoeducation program, the cognitive behavioural program included skills practice repetition and review of previous learning skills. Thus, the psychologists directed the content to oriented solutions for the difficulties that the patients presented Duration 12 weeks. Concurrent medication/care: At the start of treatment everyone used medication (metilfenidate N=13, Atomoxetine N=2, Bupropion N=0)
Funding	Academic or government funding (Departament de Salut, Government of Catalonia, and from ADANA Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + PSYCHOEDUCATION versus MIXED MEDICATION + CBT

Protocol outcome 1: Quality of life at <3 months
- Actual outcome for Adults over 18: Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) at 20 weeks PT; Group 1: mean 207.35 (SD 80.47); n=17, Group 2: mean 240.49 (SD 113.25); n=15
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Marital status, Employment, level of education, ADHD-type, type of medication.; Group 1 Number missing: 2, Reason: In PE group 1 dropped out after 5 sessions due to timetable incompatibilities, 1

Study	Estrada 2013[13]
	lost to FU because he did not turn up for PT assessment. ; Group 2 Number missing: 4, Reason: In the CBT group 1 dropped out due to illness at sessions 6, and 3 lost at FU because they missed the PT evaluation. Protocol outcome 2: ADHD symptoms (total) at <3 months - Actual outcome for Adults over 18: ADHD-RS at 20 weeks PT; Group 1: mean 24.29 (SD 9.89); n=17, Group 2: mean 25.6 (SD 10.85); n=15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Marital status, Employment, level of education, ADHD-type, type of medication.; Group 1 Number missing: 2, Reason: In PE group 1 dropped out after 5 sessions due to timetable incompatibilities, 1 lost to FU because he did not turn up for PT assessment. ; Group 2 Number missing: 4, Reason: In the CBT group 1 dropped out due to illness at sessions 6, and 3 lost at FU because they missed the PT evaluation. Protocol outcome 3: ADHD symptoms - Inattention at <3 months - Actual outcome for Adults over 18: CAARS-S inattention subscale at 20 weeks PT; Group 1: mean 18.58 (SD 8.55); n=17, Group 2: mean 19.93 (SD 8.63); n=15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Marital status, Employment, level of education, ADHD-type, type of medication.; Group 1 Number missing: 2, Reason: In PE group 1 dropped out after 5 sessions due to timetable incompatibilities, 1 lost to FU because he did not turn up for PT assessment. ; Group 2 Number missing: 4, Reason: In the CBT group 1 dropped out due to illness at sessions 6, and 3 lost at FU because they missed the PT evaluation. Protocol outcome 4: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: CAARS-S hyperactivity subscales at 20 weeks PT; Group 1: mean 13.88 (SD 9.05); n=17, Group 2: mean 15.6 (SD 8.62); n=15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Marital status, Employment, level of education, ADHD-type, type of medication.; Group 1 Number missing: 2, Reason: In PE group 1 dropped out after 5 sessions due to timetable incompatibilities, 1 lost to FU because he did not turn up for PT assessment. ; Group 2 Number missing: 4, Reason: In the CBT group 1 dropped out due to illness at sessions 6, and 3 lost at FU because they missed the PT evaluation. - Actual outcome for Adults over 18: CAARS-S impulsivity subscales at 20 weeks PT; Group 1: mean 14.76 (SD 9.13); n=17, Group 2: mean 17.6 (SD 8.46); n=15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Marital status, Employment, level of education, ADHD-type, type of medication.; Group 1 Number missing: 2, Reason: In PE group 1 dropped out after 5 sessions due to timetable incompatibilities, 1 lost to FU because he did not turn up for PT assessment. ; Group 2 Number missing: 4, Reason: In the CBT group 1 dropped out due to illness at sessions 6, and 3 lost at FU because they missed the PT evaluation. Protocol outcome 5: Emotional dysregulation at <3 months

Study	Estrada 2013[13]
- Actual outcome for Adults over 18: BDI at 20 weeks PT; Group 1: mean 13.64 (SD 12.38); n=17, Group 2: mean 12.4 (SD 11.07); n=15 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Marital status, Employment, level of education, ADHD-type, type of medication.; Group 1 Number missing: 2, Reason: In PE group 1 dropped out after 5 sessions due to timetable incompatibilities, 1 lost to FU because he did not turn up for PT assessment. ; Group 2 Number missing: 4, Reason: In the CBT group 1 dropped out due to illness at sessions 6, and 3 lost at FU because they missed the PT evaluation.	
Protocol outcomes not reported by the study	Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Ferrin 2014[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=81)
Countries and setting	Conducted in Spain; Setting: Child and Adolescent Mental health service
Line of therapy	1st line
Duration of study	Intervention + follow up: 64 weeks (12 weeks PT and 52 FU)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Schedule for Affective Disorders and Schizophrenia for school age children (KSADS-PL)
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of ADHD any subtype according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition DSM-IV; the diagnosis was confirmed by clinical interview with a child psychiatrist, supplemented with structured interview using the validated Spanish version of the semi-structured clinical interview of the Schedule for Affective Disorders and Schizophrenia for school age children (KSADS-PL , (2) age of child between 3 and 19 years, either sex, (3) informed consent of the parents and the children available; (4) parents' age greater than or equal to 18 years, (5) responsibility and legal capacity in parents, (6) participant on clinical ADHD symptoms stabilization for at least 1 month before entering the study, with most of their comorbidity represented (except for the exclusion criteria and including autistic spectrum disorders with mild

Study	Ferrin 2014[17]
	severity), and any treatment prescribed. In those receiving medication, doses had been previously adjusted to a maximum of 1.5 mg/kg/day, according to their clinical response defined by the ADHD Rating Scale.
Exclusion criteria	(1) severe intellective disabilities (IQ\70); (2) severe autistic spectrum disorders; (3) subjects with any clinically significant or unstable medical or psychiatric condition; (4) and children whose families had received any school-based individual and/or group psychosocial treatments at any point in time
Recruitment/selection of patients	Child and Adolescent Mental health service
Age, gender and ethnicity	Age - Mean (SD): 10.65 (3). Gender (M:F): 65/16. Ethnicity: 100% White European
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (PSY versus Control= CPRS inattention (mean (SD)) 9.41 (4.54) versus 10.48 (3.44); CPRS hyperactivity (mean (SD)) 8.07 (5.34) versus 8.17 (4.05)). 2. Age: Children 6-12 (Inclusion between 3 and 19 years; sample mean (SD): 10.65 (3))). 3. Previous treatment: Not stated / Unclear
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Pharma + non-pharma - Mixed medication + coaching/mentoring/psychoeducation/counselling. The (family) psychoeducation program was developed according to the basic principles and requirements for an educational program; it was adapted and implemented from a previous evidence-based program developed for patients with Bipolar Disorder. The psychoeducation group was composed of five successive groups of 8–10 families who received 12-week 90 min weekly sessions; families were educated on the disorder during the first nine sessions and finally very briefly introduced to a range of behavioural strategies for managing ADHD symptoms and reducing defiant behaviour during the last three. The integrity of the psychoeducation sessions was guaranteed by a manual that explicitly outlined all the procedures to be used in the intervention. Sessions were audiotaped and an independent person reviewed through a checklist that the different groups received an equivalent set of information. Parents received no further parental training or behavioural strategies as the aim of the program was purely educational; nevertheless they were given the opportunity to express their own experiences and feelings about their child and the impact that the child's condition had had on them. At the end of each session a hand-out was delivered. . Duration 12 weeks. Concurrent medication/care: 36 children were treated with medication at the beginning of the trial (n=37) Intervention 2: Pharma + non-pharma - Other. [Attention control] The parent-support group consisted of another five successive groups of 8–10 families who received 12-week 90 min weekly sessions; these families were reunited and encouraged to comment on their thoughts and share their experiences in a nondirective, nonthreatening environment. In this case, the therapist was not allowed to provide formal

Study	Ferrin 2014[17]
	psychotherapy or specific psychoeducation and families did not receive any specific educational material. The therapist was not allowed to give any feedback or additional information, but to guide the groups and allow everyone to express and to give their personal point of view. The use of an active control ensured that the benefits observed were mainly due to the psychoeducation programme only. It was justified on the grounds that the two groups were selected from the same clinic, were treated by the same clinicians and that the conditions at the baseline were exactly the same. The same therapist undertook all sessions in both groups and at the same clinic; once again an independent observer checked for treatment integrity in order to avoid an unfavourable reaction in the control group that biased results. Duration 12 weeks. Concurrent medication/care: 36 children were treated with medication at the beginning of the trial
Funding	Academic or government funding (Instituto de Salud Carlos III (ETS 07/90902, BAE 09/90088), the South London and Maudsley NHS Charitable Funds, Consejeria de Salud Junta de Andalucia (EF-0029), Gobierno de Navarra (Beca Ayanz) and Fundacion Alicia Koplowitz)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + PSYCHOEDUCATION versus MIXED MEDICATION VERSUS NSST

Protocol outcome 1: ADHD symptoms - Inattention at <3 months
- Actual outcome for Children and young people 5 to 18: Conners' Parent Rating Scale Revised 27-items version (CPRS-R:S) inattention subscale at 12 weeks PT; Group 1: mean 7.95 (SD 3.84); n=42, Group 2: mean 11 (SD 3.28); n=36
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself.
Two families in the psychoeducation group could not complete the one-year follow-up due to work
; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: Conners' Parent Rating Scale Revised 27-items version (CPRS-R:S) inattention subscale at 64 weeks FU; Group 1: mean 8.26 (SD 4.3); n=40, Group 2: mean 10.41 (SD 3.62); n=36
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself.

Study	Ferrin 2014[17]
	Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: Conners' Parent Rating Scale Revised 27-items version (CPRS-R:S) hyperactivity subscale at 12 weeks PT; Group 1: mean 6.74 (SD 4.84); n=42, Group 2: mean 8.45 (SD 4); n=36 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself. Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work Protocol outcome 4: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: Conners' Parent Rating Scale Revised 27-items version (CPRS-R:S) hyperactivity subscale at 64 weeks FU; Group 1: mean 7.4 (SD 4.84); n=40, Group 2: mean 8.47 (SD 3.82); n=36 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself. Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work Protocol outcome 5: Behaviour/function at <3 months - Actual outcome for Children and young people 5 to 18: Conners' Parent Rating Scale Revised 27-items version (CPRS-R:S) opposition subscale at 12 weeks PT; Group 1: mean 4.95 (SD 3.79); n=42, Group 2: mean 6.18 (SD 3.87); n=36 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself. Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work

Study	Ferrin 2014[17]
	Protocol outcome 6: Behaviour/function at >3 months - Actual outcome for Children and young people 5 to 18: Conners' Parent Rating Scale Revised 27-items version (CPRS-R:S) opposition subscale at 64 weeks FU; Group 1: mean 5.2 (SD 4.06); n=40, Group 2: mean 5.63 (SD 3.86); n=36 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself. Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work Protocol outcome 7: Emotional dysregulation at <3 months - Actual outcome for Children and young people 5 to 18: SDQ Spanish version is a 25-item behavioural screening questionnaire subscale emotional symptoms at 12 weeks PT; Group 1: mean 3.39 (SD 2.5); n=42, Group 2: mean 3.5 (SD 2.4); n=36 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself. Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work Protocol outcome 8: Emotional dysregulation at >3 months - Actual outcome for Children and young people 5 to 18: SDQ Spanish version is a 25-item behavioural screening questionnaire subscale emotional symptoms at 64 weeks FU; Group 1: mean 3.46 (SD 2.27); n=42, Group 2: mean 3.75 (SD 2.3); n=36 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4, Reason: Two families withdrew from the psychoeducation group due to the fact that the child presented with more autistic spectrum disorder traits, rather than dissatisfaction with the program itself. Two families in the psychoeducation group could not complete the one-year follow-up due to work ; Group 2 Number missing: 1, Reason: One family in the control group could not complete the one-year follow-up due to work
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Gelade 2016[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in Netherlands; Setting: Outpatient
Line of therapy	1st line
Duration of study	Intervention time: 10-12 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Teacher rating on Disruptive Behavior Disorders Rating Scale (DBDRS)
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Dutch speaking children, 7-13 years of age, with a primary clinical diagnosis of ADHD.
Exclusion criteria	Neurologic disorders and intelligence quotient (IQ) below 80
Recruitment/selection of patients	Outpatient
Age, gender and ethnicity	Age - Mean (SD): 9.63 (1.76). Gender (M:F): 85/27. Ethnicity: Not reported
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (DBDRS Parent, mean (SD): Inattention 16.24 (5.30) Hyperactivity/Impulsivity 13.73 (6.12)). 2. Age: Children 6-12 3. Previous treatment: Not stated / Unclear (At study entry, all children were free of stimulant use for at least 1 month .).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Neurofeedback. Neurofeedback and physical activity interventions consisted of 3 individual training sessions a week, with each session lasting 45 minutes including 20 min. of effective training, over a period of 10-12 weeks. Neurofeedback. Theta/beta training was applied with the aim to inhibit theta (4-8 Hz) and reinforce beta (13-20 Hz) activity at Cz. The mean number of training sessions of participants who completed the assessments at post intervention (n = 38) was 29 (mean = 28.53; SD = 2.63; range, 19-30 sessions) .

Study	Gelade 2016[20]
	Theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/ beta index as averaged over l trial relative to session baseline was rewarded with the appearance of a sun and yielded credits. To promote generalization of the learned strategies into daily life, transfer trials were used. Transfer trials were presented without immediate visual feedback and were included from session 11 (25%) and session 21 (50%) onward. To further transfer learned behaviours, participants were instructed to retrieve their neurofeedback experiences by watching printed graphics of the training during school and homework. Compliance was verified by questioning the participants as to whether they used the transfer cards over the intervention period. Transfer cards were used by 84% of the participants. . Duration 10-12 weeks. Concurrent medication/care: Unclear (n=36) Intervention 2: CNS stimulants - Methylphenidate. A 4-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate. 25 The titration phase was preceded by a baseline week to determine ADHD symptoms without methylphenidate and was followed by a lead-in week in which on 3 consecutive days, twice-daily (at breakfast and lunchtime) , doses of (1) 5 mg, (2) 10 mg, and (3) 15 mg (25 kg body weight) or 20 mg of methylphenidate (> 25 kg body weight) were used to assess possible adverse effects. During the 4-week titration phase, children received in pseudorandom order (1) 5 mg, (2)10 mg, or (3) 15 mg or 20 mg of methylphenidate or (4) placebo for 1 week, twice daily. During the titration phase, children, parents, and teachers as well as the researchers were blinded with regard to the prescribed dose (placebo non responders were treated with 5 mg of methylphenidate twice daily. The child's psychiatrist prescribed the optimal dose of methylphenidate for the remaining intervention period (5 mg to 10 children including 8 responders and 2 non-responders, 10 mg to 14 children, 15 mg to 2 children, and 20 mg to 5 children). . Duration 10-12 weeks. Concurrent medication/care: Unclear (n=37) Intervention 3: Exercise. Neurofeedback and physical activity interventions consisted of 3 individual training sessions a week, with each session lasting 45 minutes including 20 min. of effective training, over a period of 10-12 weeks. Maximum heart rate (HRmax) was determined before the start of the first training session a standard HRmax test. Each training session started with 5 minutes of warming up, followed by five 2-minute moderate intensity exercises at a level of 70%-80% of HRrnax. After a 5 minute break, five 2-minute vigorous intensity exercises 80%- 100% of HRmax were performed Each training finished with a 5-minute cool down. Time and heart monitored and registered using a Polar FT4 watch (Polar Electro Oy, Kempele, Finland). The

Study	Gelade 2016[20]
	mean number of sessions of participants who completed the assessments at post-intervention (n = 34) was 28 (mean = 27.74; SD = 3.56; range, 12-30) Duration 10-12 weeks. Concurrent medication/care: Unclear
Funding	This trial is funded by the Netherlands Organization for Health Research and Development (ZonMw): 157 003012.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NEUROFEEDBACK versus METHYLPHENIDATE

Protocol outcome 1: ADHD symptoms - Inattention at <3 months
- Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Inattention (Teacher)

at 10-12 weeks PT; Group 1: mean 1.3 (SD 0.76); n=39,
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Unclear
- Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Inattention (Parent)

at 10-12 weeks PT; Group 1: mean 1.11 (SD 0.67); n=39,
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: ADHD symptoms - Hyperactivity at <3 months
- Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Hyper/Impuls (Parent)

at 10-12 weeks PT; Group 1: mean 1.02 (SD 0.81); n=39,
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Gelade 2016[20]
Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Hyper/Impuls (Teacher) at 10-12 weeks PT; Group 1: mean 1.16 (SD 1.11); n=39, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Unclear RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE versus EXERCISE Protocol outcome 1: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Inattention (Parent) at 10-12 weeks PT; Group 1: mean 0.61 (SD 0.83); n=36, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Inattention (Teacher) at 10-12 weeks PT; Group 1: mean 0.57 (SD 0.79); n=33, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Unclear Protocol outcome 2: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Hyper/Impuls (Parent) at 10-12 weeks PT; Group 1: mean 0.62 (SD 0.9); n=36,

Study	Gelade 2016[20]
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Children and young people 5 to 18: Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) scale - Hyper/Impuls (Teacher) at 10-12 weeks PT; Group 1: mean 0.23 (SD 0.9); n=33, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Age, Sex and ADHD symptoms; Group 1 Number missing: 0; Group 2 Number missing: 3, Reason: Unclear	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Handen 2015[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=128)
Countries and setting	Conducted in USA; Setting: outpatient
Line of therapy	1st line
Duration of study	Intervention time: 10 weeks (PT)
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: significant symptoms of overactivity and/or inattention at both home and school, based upon a mean item score ≥ 1.50 on the parent- and teacher-completed Swanson, Nolan, and Pelham (SNAP) scales and a Clinical Global Improvement (CGI) -Severity score ≥4.
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable

Study	Handen 2015[21]
Inclusion criteria	Between 5.0 and 14.11 years old, both male and female, with a minimum mental age (MA) of 24 months. All participants met criteria for an ASD (autistic disorder, Asperger's disorder, pervasive developmental disorder-not otherwise specified [PDD-NOS]), based upon the Autism Diagnostic Interview–Revised and expert clinical evaluation using a DSM-IV-TR interview. Participants also exhibited significant symptoms of overactivity and/or inattention at both home and school, based upon a mean item score ≥ 1.50 on the parent- and teacher-completed Swanson, Nolan, and Pelham (SNAP) scales and a Clinical Global Improvement (CGI) -Severity score ≥4.
Exclusion criteria	Exclusion criteria included Rett's disorder, childhood disintegrative disorder, lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar disorder, or current diagnosis of major depression or obsessive-compulsive disorder. Children with significant medical conditions (e.g., heart, liver, renal, or pulmonary disease) or significant abnormalities on routine laboratory tests and electrocardiogram (ECG) were excluded. Other exclusion criteria included a prior adequate trial of ATX (minimum of four weeks, with at least one week at ≥ 1.0 mg/kg) within the last two years, and regular usage of beta adrenergic blocking agents, asthma medicine, such as albuterol (because of potential for drug interaction), and prior involvement in a highly structured parent training program.
Recruitment/selection of patients	no further information
Age, gender and ethnicity	Age - Mean (SD): 8.1 (2.1) . Gender (M:F): 109/19. Ethnicity: 82% Caucasian, 8% African American, 8% Multi-Racial, and 2% Other
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (5-14 years). 3. Previous treatment: Not stated / Unclear
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Pharma + non-pharma - Atomoxetine + carer/family +/- teacher training. parental training (PT): Families assigned to PT met weekly for individual sessions with a PT clinician. Sessions were adapted from the RUPP Parent Manual and covered topics such as preventing behaviour problems, reinforcement, time out, and planned ignoring. Each session lasted 60–90 minutes and included didactic materials, videos, and role playing. PT clinicians were trained by supervisors who were licensed clinical psychologists with specialized training in behavioural interventions and developmental disabilities ATX doses were split twice daily to prevent side effects. Once-daily dosing was allowed if strongly preferred by a given family. ATX doses were individually adjusted according to a weight-based dosage schedule, with medical clinicians allowed to delay increases or to reduce doses due to AEs. The initial dose was 0.3mg/kg/day

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	(rounded to the nearest 5 mg) with weekly escalations by 0.3mg/kg/day, unless there were limiting side effects or no further room for improvement, to a target dose of 1.2 mg/kg/day, and could be increased to a maximum of 1.8 mg/kg/day based on clinical status and response . Duration 24 weeks (FU). Concurrent medication/care: - (n=32) Intervention 2: Atomoxetine. ATX doses were split twice daily to prevent side effects. Once-daily dosing was allowed if strongly preferred by a given family. ATX doses were individually adjusted according to a weight-based dosage schedule, with medical clinicians allowed to delay increases or to reduce doses due to AEs. The initial dose was 0.3mg/kg/day (rounded to the nearest 5 mg) with weekly escalations by 0.3mg/kg/day, unless there were limiting side effects or no further room for improvement, to a target dose of 1.2 mg/kg/day, and could be increased to a maximum of 1.8 mg/kg/day based on clinical status and response. Duration 24 weeks (FU). Concurrent medication/care: - (n=32) Intervention 3: Carer and family training problem - Without involvement of person with ADHD. Families assigned to PT met weekly for individual sessions with a PT clinician. Sessions were adapted from the RUPP Parent Training Manual and covered topics such as preventing behaviour problems, reinforcement, time out, and planned ignoring. Each session lasted 60–90 minutes and included didactic materials, videos, and role playing. PT clinicians were trained by supervisors who were licensed clinical psychologist with specialized training in behavioural interventions and developmental disabilities placebo. Duration 24 weeks. Concurrent medication/care: - (n=32) Intervention 4: Placebo/usual care. placebo, no further details. Duration 24 weeks. Concurrent medication/care: unknown
Funding	Academic or government funding (supported by grants from the National Institute of Mental Health to Ohio State University (5R01MH079080), University of Pittsburgh (5R01MH079082-05), and University of Rochester (5R01 MH083247), by Eli Lilly and Co., who provided atomoxetine and placebo, and by the University of Rochester CTSA (UL1 RR024160) and Ohio State University CTSA (UL1TR001070) from the National Center for Research Resources and the National Center for Advancing Translational Sciences of the National Institutes of Health.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE + PARENT TRAINING versus ATOMOXETINE

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.23 - (SD 0.69); n=32, Group 2: mean 1.24 - (SD 0.56); n=32; SNAP-IV, Swanson, Nolan, and Pelham 0-54 Top=High is poor outcome; Comments: number of patients for each

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arm was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.14 - (SD 0.82); n=32, Group 2: mean 1.49 - (SD 0.74); n=32; Swanson, Nolan, and Pelham, SNAP-IV, 0-54 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.3 - (SD 0.72); n=32, Group 2: mean 1.36 - (SD 0.61); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.3 - (SD 0.85); n=32, Group 2: mean 1.66 - (SD 0.78); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.15 - (SD 0.74); n=32, Group 2: mean 1.12 - (SD 0.65); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity/impulsivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 0.98 - (SD 0.92); n=32, Group 2: mean 1.32 - (SD 0.92); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity/impulsivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: CGI-I at <3 months - Actual outcome for Children and young people 5 to 18: CGI≤2 at 10 weeks; Group 1: 15/31, Group 2: 15/32 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE + PARENT TRAINING versus PARENT TRAINING + PLACEBO Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.14 - (SD 0.82); n=32, Group 2: mean 1.46 - (SD 0.82); n=32; Swanson, Nolan, and Pelham, SNAP-IV, 0-54 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.23 (SD 0.69); n=32, Group 2: mean 1.45 (SD 0.62); n=32; Swanson, Nolan, and Pelham, SNAP-IV, 0-54 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.3 - (SD 0.72); n=32, Group 2: mean 1.45 - (SD 0.71); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.3 - (SD 0.85); n=32, Group 2: mean 1.64 - (SD 0.82); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.15 (SD 0.74); n=32, Group 2: mean 1.44 (SD 0.72); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity/impulsivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 0.98 - (SD 0.92); n=32, Group 2: mean 1.28 - (SD 0.99); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity/impulsivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: CGI-I at <3 months - Actual outcome for Children and young people 5 to 18: CGI≤2 at 10 weeks; Group 1: 15/31, Group 2: 9/31 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE + PARENT TRAINING versus PLACEBO Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.23 (SD 0.69); n=32, Group 2: mean 1.74 (SD 0.86); n=32; Swanson, Nolan, and Pelham, SNAP-IV 0-54 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.14 (SD 0.82); n=32, Group 2: mean 1.44 (SD 0.85); n=32; Swanson, Nolan, and Pelham, SNAP-IV 0-54 Top=High is poor outcome; Comments: number of patients for each arm was not reported; Intention to treat analysis, so probably,

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	all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.3 (SD 0.72); n=32, Group 2: mean 1.79 (SD 0.84); n=32; Swanson, Nolan, and Pelham, SNAP-IV subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm was not reported; Intention to treat analysis, so probably, all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.3 (SD 0.85); n=32, Group 2: mean 1.63 (SD 0.98); n=32; Swanson, Nolan, and Pelham, SNAP-IV subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm was not reported; Intention to treat analysis, so probably, all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.15 (SD 0.74); n=32, Group 2: mean 1.69 (SD 0.97); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm was not reported; Intention to treat analysis, so probably, all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 0.98 (SD 0.92); n=32, Group 2: mean 1.25 (SD 0.92); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm was not reported;

Study	Handen 2015[21]
Intention to treat analysis, so probably, all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: CGI-I at <3 months - Actual outcome for Children and young people 5 to 18: CGI≤2 at 10 weeks; Group 1: 15/31, Group 2: 6/31 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENT TRAINING + PLACEBO versus ATOMOXETINE Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.45 - (SD 0.62); n=32, Group 2: mean 1.24 - (SD 0.56); n=32; Swanson, Nolan, and Pelham, SNAP-IV, 0-54 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms total, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.46 - (SD 0.82); n=32, Group 2: mean 1.49 - (SD 0.74); n=32; Swanson, Nolan, and Pelham, SNAP-IV, 0-54 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.45 - (SD 0.71); n=32, Group 2: mean 1.36 - (SD 0.61); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.64 - (SD 0.82); n=32, Group 2: mean 1.66 - (SD 0.78); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale inattention 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included.

Study	Handen 2015[21]
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Parent) at 10 weeks; Group 1: mean 1.15 - (SD 0.74); n=32, Group 2: mean 1.44 - (SD 0.72); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity/impulsivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity, SNAP-IV (Teacher) at 10 weeks; Group 1: mean 1.28 (SD 0.99); n=32, Group 2: mean 1.32 (SD 0.92); n=32; Swanson, Nolan, and Pelham, SNAP-IV, subscale hyperactivity/impulsivity 0-27 Top=High is poor outcome; Comments: number of patients for each arm in the analyses was not reported; Intention to treat analysis, so probably, all patients were included. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: CGI-I at <3 months - Actual outcome for Children and young people 5 to 18: CGI≤2 at 10 weeks; Group 1: 9/31, Group 2: 15/32 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: -- ; Baseline details: % with severe ADHD (CGI), placebo 34%, parent training+ placebo 19%, ATX 25%, ATX + parental training 13%; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Hiscock 2015[24]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=244)

Study	Hiscock 2015[24]
Countries and setting	Conducted in Australia; Setting: 21 general paediatric practices in Victoria, Australia
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) cross situational impairment in two or more of home, school, or social settings (2) had parent reported moderate to severe sleep problems; and met the American Academy of Sleep Medicine diagnostic criteria for at least one sleep disorder (for example, sleep onset association disorder, limit setting disorder, delayed sleep phase, or idiopathic or psychophysiological insomnia) or anxiety leading to insomnia.
Exclusion criteria	(1) specialised sleep assistance from a psychologist or a sleep clinic, or had a serious medical condition (for example, severe cerebral palsy) (2) intellectual disability (paediatrician record of IQ <70) (3) suspected obstructive sleep apnoea assessed using the corresponding subscale from the children's sleep habits questionnaire,16 and their parents had insufficient English to complete surveys.
Recruitment/selection of patients	Families with a child aged 5 to 12 years who had been seen within the past year for ADHD were contacted (Between August 2010 and June 2012)
Age, gender and ethnicity	Age - Range: 5-12 years. Gender (M:F): 208/170. Ethnicity: Not specified
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (Mean baseline ADHD-RS score of 36). 2. Age: Children 6-12 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=122) Intervention 1: Pharma + non-pharma - Other. 2 face to face, fortnightly consultations about sleep with a trained clinician (five psychologists; four with 1-4 years of clinical experience and one with 10 years, or a trainee consultant paediatrician with four years of paediatric clinical experience) at their paediatrician's office, the hospital clinic, or home. Families were offered one follow-up telephone call two weeks later. The clinicians' training consisted of two three hour sessions, conducted by HH and ES, and included information on normal sleep, sleep cycles, sleep cues, sleep hygiene (that is, set bed time, bedtime routines, keeping the bedroom media-free, and avoiding caffeine consumption after 3 pm), and standard management strategies for behaviour known to be effective in typically developing children. At the first consultation, the clinician assessed the child's sleep problem, elicited parent goals for sleep management, provided information about normal sleep, sleep cycles, and sleep hygiene strategies, and formulated a behavioural sleep management plan tailored to the child's sleep problem. For example, limit setting disorder was managed by ignoring child protests and rewarding compliance with bedtime routines. Delayed sleep phase was managed using bedtime

Study	Hiscock 2015[24]
	fading whereby the child's bedtime is temporarily set later and gradually brought forward, while continuing to wake the child at a preset time in the morning. Anxiety related insomnia was managed by visual imagery and relaxation techniques. Parents were asked to complete a sleep diary between the first and second consultation. The second consultation and follow-up telephone call were used to review the sleep diary, reinforce suggested strategies, and troubleshoot any problems. . Duration 4 weeks. Concurrent medication/care: 88% on ADHD medication (n=122) Intervention 2: Mixed medication - Non-specific medication. Usual care. Duration 4 weeks. Concurrent medication/care: 88%on ADHD medication
Funding	Academic or government funding (Australian National Health and Medical Research Council)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + SLEEP INTERVENTION versus NON-SPECIFIC MEDICATION

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms total - teacher reported ARS-IV scale 3 months PT at 3 months; Mean; -2.4 (95%CI -5.3 to 0.4);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children and young people 5 to 18: ADHD symptoms total - parent reported ARS-IV scale - 3 months PT at 3 months; Mean; -3.7 (95%CI -6.1 to -1.2);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms total - parent reported ARS-IV scale - 6 months PT at 6 months; Mean; -3.9 (95%CI -6.3 to -1.5);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Children and young people 5 to 18: ADHD symptoms total - teacher reported ARS-IV scale 6 months PT at 6 months; Mean; -2.4 (95%CI -5.8 to 1);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: ADHD symptoms - Inattention at <3 months

Study	Hiscock 2015[24]
- Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention - parent reported ARS-IV scale 3 months PT at 3 months; Mean; -2.4 (95%CI -3.8 to -1); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention - teacher reported ARS-IV scale 3 months PT at 3 months; Mean; -0.7 (95%CI -2.3 to 0.8); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: ADHD symptoms - Inattention at >3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention - parent reported ARS-IV scale 6 months PT at 6 months; Mean; -2.4 (95%CI -3.7 to -1); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention - teacher reported ARS-IV scale 6 months PT at 6 months; Mean; -0.9 (95%CI -2.9 to 1, Comments: Change score); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity/impulsivity - parent reported ARS-IV scale 3 months PT at 3 months; Mean; -1.3 (95%CI -2.5 to 0); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity/impulsivity - teacher reported ARS-IV scale 3 months PT at 3 months; Mean; -1.8 (95%CI -3.4 to -0.2, Units: Change score); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity/impulsivity - parent reported ARS-IV scale 6 months PT at 6 months; Mean; -1.5 (95%CI -2.8 to -0.2); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity/impulsivity - teacher reported ARS-IV scale 6 months PT at 6 months; Mean; -1.4 (95%CI -3.3 to 0.4); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,	

Study	Hiscock 2015[24]
Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Behaviour/function at <3 months - Actual outcome for Children and young people 5 to 18: Behaviour - teacher reported Strengths and difficulties questionnaire 3 months PT at 3 months; Mean; -1.7 (95%CI -3.4 to -0.1); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Behaviour/function at >3 months - Actual outcome for Children and young people 5 to 18: Behaviour - teacher reported Strengths and difficulties questionnaire 6 months PT at 6 months; Mean; -2.4 (95%CI -4.3 to -0.5); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study (subsidiary papers)	Jans 2015-1[26] (Jans 2013[25])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in Germany; Setting: The study was performed at five specialized university study sites
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL)

Study (subsidiary papers)	Jans 2015-1[26] (Jans 2013[25])
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	• diagnosis of ADHD according to DSM-IV criteria • age 6–12 years, inclusive • no medication or on stable medication since at least 4 weeks before baseline assessment
Exclusion criteria	All patients • interventions under investigation for the treatment of ADHD within the last 6 months before baseline (mothers: psychotherapy for ADHD, MPH; children: parent–child training) • necessity of inpatient treatment • insufficient German language skills • I.Q. ≤ 80 • pervasive developmental disorder, psychosis, schizophrenia, bipolar disorder, severe depressive episode
Recruitment/selection of patients	The participants were primarily recruited from clinical samples from the departments of child psychiatry. In addition, local child psychiatrists were asked to refer patients, and the trial was described in local newspapers and on websites to allow for self-referral.
Age, gender and ethnicity	Age - Mean (SD): 9.45 (1.7). Gender (M:F): 105/39. Ethnicity:
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 3. Previous treatment: (no medication or on stable medication, Approximately, three-quarters of the children entered the trial on stable medication for the treatment of ADHD (TG: 57/77, 74.0%; CG: 50/66, 75.8%).).
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Carer and family training problem - With involvement of person with ADHD. Mothers with ADHD were also part of the study and received the PCT intervention and were randomised to the treatment group (TG) they received multimodal treatment (cognitive behavioural group psychotherapy (GPT) plus pharmacotherapy with MPH). All children received behavioural parent–child training (PCT). PCT was conducted using a therapy program for children with hyperkinetic and oppositional problem behaviour (THOP), which is a structured modular behavioural psychotherapy program). The effectiveness of this program was demonstrated in an adaptive trial on the treatment of childhood ADHD. The treatment modules focused on developing a functional model of problem behaviour, setting treatment goals, enhancing positive parent–child interactions, controlling hyperkinetic and oppositional behaviour (e.g. addressing demands effectively, setting positive and negative consequences consistently, and using token economies, response cost, and time out), and self-management training. As much as possible, the child's teacher and the child's father or the mother's partner were involved. PCT was administered during individual 1-hr sessions that predominantly involved the child and

Study (subsidiary papers)	Jans 2015-1[26] (Jans 2013[25])
	mother. In all, 12 weekly sessions and two booster sessions took place. Duration 52 weeks (TG). Concurrent medication/care: Any psychopharmacological treatment 74.0% (n=57) ; Psychoanaleptics 74.0% (n=57) ; Psycholeptics 1.3% (n=1) ; Antiepileptics 2.6% (n=2) (n=66) Intervention 2: Carer and family training problem - With involvement of person with ADHD. Mothers with ADHD were also part of the study and received the PCT intervention and were randomised to the control group (CG) received clinical management (CM), which included supportive counselling without any specific pharmacological or psychotherapeutic interventions. All children received behavioral parent–child training (PCT). PCT was conducted using a therapy program for children with hyperkinetic and oppositional problem behavior (THOP), which is a structured modular behavioral psychotherapy program). The effectiveness of this program was demonstrated in an adaptive trial on the treatment of childhood ADHD. The treatment modules focused on developing a functional model of problem behavior, setting treatment goals, enhancing positive parent–child interactions, controlling hyperkinetic and oppositional behavior (e.g. addressing demands effectively, setting positive and negative consequences consistently, and using token economies, response cost, and time out), and self-management training. As much as possible, the child's teacher and the child's father or the mother's partner were involved. PCT was administered during individual 1-hr sessions that predominantly involved the child and mother. In all, 12 weekly sessions and two booster sessions took place. Duration 52 weeks (CG). Concurrent medication/care: Any psychopharmacological treatment 75.8% (n=50); Psychoanalepticsd 75.8% (n=50); Psycholeptics 4.5% (n=3); Antiepileptics 1.5% (n=1)
Funding	Academic or government funding (German Federal Ministry of Education and Research (BMBF; 01GV0605, 01GV0606).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WITH INVOLVEMENT OF PERSON WITH ADHD versus WITH	

Study (subsidiary papers)	Jans 2015-1[26] (Jans 2013[25])
INVOLVEMENT OF PERSON WITH ADHD Protocol outcome 1: ADHD symptoms (total) at >3 months - Actual outcome for Children and young people 5 to 18: SDQ subscale hyperactivity and inattention (range: 0–10), mother at 52 weeks PT; Group 1: mean 5.7 (SD 1.76); n=77, Group 2: mean 6.2 (SD 2.04); n=66; SDQ subscale hyperactivity and inattention, mother 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, ADHD-type, IQ , Comorbid behavioral disorders, Children taking medication. ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Emotional dysregulation at >3 months - Actual outcome for Children and young people 5 to 18: SDQ subscale emotional symptoms (range: 0–10), mother at 52 weeks PT; Group 1: mean 3.3 (SD 1.11926); n=77, Group 2: mean 3.1 (SD 0.932606); n=66; SDQ subscale emotional symptoms, mother 0-10 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, ADHD-type, IQ , Comorbid behavioral disorders, Children taking medication. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Jans 2015-2[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in Germany; Setting: The study was performed at five specialized university study sites
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic checklist for diagnosis of ADHD in adults (ADHS-DC), Wender-Utah Rating Scale-German short version (WURSk), Structured Clinical Interview for DSM-IV (SCID-I, SCID-II).
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	• diagnosis of ADHD according to DSM-IV criteria • age 18–60 years, inclusive • Wender-Utah Rating Scale, short version: score ≥ 30 • no pathological abnormality detected on physical examination, routine blood testing (blood count, renal, hepatic, and thyroid function), ECG, and EEG
Exclusion criteria	• interventions under investigation for the treatment of ADHD within the last 6 months before baseline (mothers: psychotherapy for ADHD, MPH; children: parent–child training) • necessity of inpatient treatment • insufficient German language skills, • I.Q. < 85 • schizophrenia, bipolar disorder, borderline personality disorder, antisocial personality disorder, suicidal or self-harming behavior, autism, motor tics, Tourette's syndrome • substance abuse/dependence within 6 months prior to screening (episodic abuse is not an exclusion criterion); positive drug screening • neurological diseases, seizures, glaucoma, uncontrolled hypertension • current eating disorder/low weight (BMI < 20) • known MPH intolerance • pregnancy or breastfeeding; no reliable contraception (Pearl Index > 1%) • other psychotherapeutic or psychopharmacological treatment
Recruitment/selection of patients	The participants were primarily recruited from clinical samples from the departments of child psychiatry. In addition, local child psychiatrists were asked to refer patients, and the trial was described in local newspapers and on websites to allow for self-referral

Study	Jans 2015-2[26]
Age, gender and ethnicity	Age - Mean (SD): 38.31 (5.69). Gender (M:F): 0/144. Ethnicity: not reported
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (CAARS-O:L: ADHD Index (Mean (SD)) 19.2 (5.7) versus 19.5 (6.1) (TG versus CG)). 2. Age: Adults 18-65 (18-60 years). 3. Previous treatment: (Mothers did not have treatment under investigation (psychotherapy for ADHD, MPH) in the last 6 months before baseline).
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Pharma + non-pharma - Stimulants + CBT. Mothers in the treatment group (TG) received multimodal treatment (cognitive behavioral group psychotherapy (GPT) plus pharmacotherapy with MPH), and mothers in the control group (CG) received clinical management (CM), which included supportive counselling without any specific pharmacological or psychotherapeutic interventions. Step 2 added PCT for all mother–child dyads for another 12 weeks. Step 3 provided 6 months of maintenance therapy for all interventions, In the TG, GPT was conducted according to a structured, manualized skills training program based on dialectical behavior therapy and cognitive behavioral therapy. The treatment steps focused on psycho-education, mindfulness training, organizational skills, self-management (functional analysis of problem behavior and principles of change), emotional regulation, impulse control, stress management, and interpersonal problems. Each GPT session lasted 120 min. Between sessions, patients completed therapeutic homework tasks and filled out a structured skills protocol. Two therapists conducted group sessions. Each closed patient group lasted for 52 weeks and included six to nine mothers. If necessary, up to three individual sessions were offered to patients in addition to the GPT sessions for individual topics that could be better addressed outside the group setting. The usefulness and feasibility of the GPT program has been demonstrated by an uncontrolled pilot study and a multicenter feasibility study by the authors of the manual and by a small RCT from an independent study group. In addition to GPT, mothers in the TG were medicated with MPH, beginning with dosages of 10 mg/d and titrating up to daily dosages not exceeding 1.3 mg/kg of a patient's body weight. Multiple doses were allowed. Individual dosages could be adjusted during the 52-week trial participation period. Because of the short half-life of MPH, our trial used a combined 50% fast release and 50% sustained release MPH medication (MedikinetTM retard) designed to deliver therapeutic plasma levels for approximately 8 hr. Behavioral parent–child training PCT was conducted using a therapy program for children with hyperkinetic and oppositional problem behavior (THOP), which is a structured modular behavioral psychotherapy

Study	Jans 2015-2[26]
	program). The effectiveness of this program was demonstrated in an adaptive trial on the treatment of childhood ADHD. The treatment modules focused on developing a functional model of problem behavior, setting treatment goals, enhancing positive parent–child interactions, controlling hyperkinetic and oppositional behavior (e.g. addressing demands effectively, setting positive and negative consequences consistently, and using token economies, response cost, and time out), and self-management training. As much as possible, the child's teacher and the child's father or the mother's partner were involved. PCT was administered during individual 1-hr sessions that predominantly involved the child and mother. In all, 12 weekly sessions and two booster sessions took place. . Duration 52 weeks. Concurrent medication/care: not reported (n=66) Intervention 2: Coaching, mentoring, psychoeducation, counselling - Counselling. Mothers in the treatment group (TG) received multimodal treatment (cognitive behavioral group psychotherapy (GPT) plus pharmacotherapy with MPH), and mothers in the control group (CG) received clinical management (CM), which included supportive counselling without any specific pharmacological or psychotherapeutic interventions. Step 2 added PCT for all mother–child dyads for another 12 weeks. Step 3 provided 6 months of maintenance therapy for all interventions, Mothers in the CG received CM that consisted of supportive counselling during individual sessions that lasted 15 to 20 min and were structured by a checklist. The session content was based on the mothers' requested themes. The physician had a supportive position during the conversations. Mothers who sought support and advice were encouraged to develop and implement individual solutions. Specific psychotherapeutic techniques or strategies were not applied. Interventions related to the GPT program for ADHD were not allowed during the CM sessions. After the end of the study treatments, individual treatment at our outpatient units for adult ADHD was offered to the patients Behavioral parent–child training PCT was conducted using a therapy program for children with hyperkinetic and oppositional problem behavior (THOP), which is a structured modular behavioral psychotherapy program). The effectiveness of this program was demonstrated in an adaptive trial on the treatment of childhood ADHD. The treatment modules focused on developing a functional model of problem behavior, setting treatment goals, enhancing positive parent–child interactions, controlling hyperkinetic and oppositional behavior (e.g. addressing demands effectively, setting positive and negative consequences consistently, and using token economies, response cost, and time out), and self-management training. As much as possible, the child's teacher and the child's father or the mother's partner were involved. PCT was administered during individual 1-hr sessions that predominantly involved the child and mother. In all, 12

Study	Jans 2015-2[26]
	weekly sessions and two booster sessions took place. . Duration 52 weeks. Concurrent medication/care: not reported
Funding	Academic or government funding (German Federal Ministry of Education and Research (BMBF; 01GV0605, 01GV0606).)

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

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Adults over 18: CAARS–O:L ADHD index (range: 0–36) (observer)

at 52 weeks (PT); Group 1: mean 13.1 (SD 5.73); n=77, Group 2: mean 15.8 (SD 5.7); n=66; CAARS–O:L ADHD index (observer) 0-36 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Marital status, ADHD-type, IQ , Comorbid behavioral disorders, intervention received in the past.

; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Adults over 18: CAARS–O:L ADHD Inattention/memory problems (range:0–36) (observer)

at 52 weeks (PT); Group 1: mean 12.4 (SD 6.17); n=77, Group 2: mean 15.1 (SD 6.51); n=66; CAARS–O:L ADHD Inattention/memory problems (observer) 0-36 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Marital status, ADHD-type, IQ , Comorbid behavioral disorders, intervention received in the past.

; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Jans 2015-2[26]
Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Adults over 18: CAARS–O:L ADHD Hyperactivity/restlessness (range: 0–36) (observer) at 52 weeks (PT); Group 1: mean 10.7 (SD 5.72); n=77, Group 2: mean 13.7 (SD 5.7); n=66; CAARS–O:L ADHD Hyperactivity/restlessness (observer) 0-36 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Marital status, ADHD-type, IQ , Comorbid behavioral disorders, intervention received in the past. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Hyperactivity at <3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study (subsidiary papers)	Konstenius 2014[34] (Konstenius 2013[35])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=54)
Countries and setting	Conducted in Sweden; Setting: Out-patient care
Line of therapy	1st line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: the Structured Clinical Interview for DSM-IV I and II (SCID I and II)
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults meeting the diagnostic criteria for ADHD according to the Diagnostic and Statistical Manual of Mental

Study (subsidiary papers)	Konstenius 2014[34] (Konstenius 2013[35])
	Disorders (DSM-IV) and the DSM-IV diagnostic criteria for amphetamine dependence during the last 12 months prior to the current incarceration, and had used amphetamines on a minimum of 12 occasions during the last 12 weeks preceding the incarceration.
Exclusion criteria	(i) DSM-IV diagnosis of any other substance dependence except nicotine, currently or during the 12 months prior to incarceration, (ii) a major psychiatric disorder (e.g. schizophrenia, severe depression), (iii) current antipsychotic medication, (iv) current use of benzodiazepine, (v) traces of any of the following substances in urine: amphetamine, benzodiazepine, cannabis, cocaine, dextropropoxyphene and opiates, (vi) serious somatic disease (e.g. moderate to severe hypertension >150/95 mm Hg, hyperthyroidism) and (vii) known hypersensitivity to methylphenidate. Prior to inclusion participants underwent a physical examination, including laboratory tests for haematology and liver function, short neurological status and a basic cardiovascular examination. At any indication of heart problems the participant was referred to a specialized heart clinic for a cardiac examination, including electrocardiogram
Recruitment/selection of patients	Prison
Age, gender and ethnicity	Age - Mean (SD): 41.5 (9,83). Gender (M:F): 54/0. Ethnicity: 93% were born in Sweden
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 3. Previous treatment: Not stated / Unclear
Extra comments	Participants from medium security prisons and co-diagnosis of ADHD and amphetamine dependence
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Pharma + non-pharma - Stimulants + CBT. The medication started 14 days before release from prison (two participants started 3 days and one 5 days before release) and continued for 24 weeks. Like the majority of prisoners in Sweden, all participants were released on supervised probation involving mandatory meetings with a probation officer. The start dose was 18 mg MPH/placebo titrated over a period of 19 days (with 36 mg increments every 3 days), to a maximum dose of 180 mg/day. For participants who did not require or tolerate a dose increase, the dosage was adjusted and continued at that level. To enhance compliance, the subjects were picked up by a prepaid taxi at the prison gate on the day of their release and taken to the out-patient clinic, where they received study medication for 2–4 days and were asked to provide a supervised urine specimen. During the 22-week out-patient treatment phase, the participants visited the clinic twice weekly to meet the research nurse who dispensed the study medication

Study (subsidiary papers)	Konstenius 2014[34] (Konstenius 2013[35])
	and supervised the urine sampling. Once weekly, for the first 12 weeks, the participants attended individual manual-based cognitive–behavioural therapy sessions targeting addiction relapse verified by patient self-reports and supervised urine toxicology Duration 24 weeks. Concurrent medication/care: none (n=27) Intervention 2: Cognitive behavioural therapies - CBT. Placebo and CBT to prevent addiction relapse (same as other arm). Duration 24 weeks. Concurrent medication/care: no other treatment
Funding	Academic or government funding (Swedish National Board of Health and Welfare, the Swedish Research Council and Stockholm County Council)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CBT versus CBT Protocol outcome 1: ADHD symptoms (total) at >3 months - Actual outcome for Adults over 18: Conners' adult ADHD self-rating scale (CAARS:SV) at 24 weeks (PT); Group 1: 17/26, Group 2: 7/26; Comments: Events of decreased symptoms of inattention or hyperactivity by at least 30%, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Marital status, ADHD-type, IQ , Substance use, criminality measures, homelessness and hepatitis status ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Lee 2017[36]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in South Korea; Setting: Korea
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Based on DSM-IV and confirmed by psychiatrist
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Not excluded
Exclusion criteria	Used medication other than for ADHD, comorbidity other than ODD or anxiety, received NF in the past, IQ <80
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 8.7 (2). Gender (M:F): 75:25. Ethnicity: Not stated
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Pharma + non-pharma - Other. Medication not stated. NF (Beta/SMR training using visual feedback reward) conducted by clinical psychologist. 20 sessions delivered twice a week, over 10 weeks. Duration 10 weeks. Concurrent medication/care: Not stated (n=18) Intervention 2: Mixed medication - Non-specific medication. Medication and nil else specified. Duration 10 weeks. Concurrent medication/care: Nil else specified
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDICATION + NF versus MEDICATION

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD rating scale, final value, parent rated at PT at 10 weeks; Group 1: mean 10.78 (SD 4.91); n=18,
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Lee 2017[36]
Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Behaviour/function at <3 months - Actual outcome for Children and young people 5 to 18: Conners BRS, final value, parent or teacher rated at PT at 10 weeks; Group 1: mean 7.61 (SD 4.9); n=18, Group 2: mean 11.33 (SD 5.03); n=18 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Levin 2007[37]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=106)
Countries and setting	Conducted in USA; Setting: Outpatient
Line of therapy	1st line
Duration of study	Intervention time: 14 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Structured clinical interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders (4th ed. [DSM-IV])
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	To meet DSM-IV criteria for cocaine dependence and persistent adult attention deficit hyperactivity disorder (ADHD).

Study	Levin 2007[37]
Exclusion criteria	(I) met DSM- IV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention, (2) were physiologically dependent on opioids, sedatives or alcohol such that medical attention was required during periods of abstinence or significant reductions in use, (3) exhibited sui-cidal or homicidal behavior within the past 2 years, (4) were prescribed any psychotropic medication, (5) had an unstable medical condition that would make participation hazardous (i.e. uncontrolled diabetes), (6) had a known sensitivity to MPH, (7) were nursing and/or pregnant and (8) were unable to give full and informed consent.
Recruitment/selection of patients	Recruited by local advertising or by referrals in the New York City metropolitan area.
Age, gender and ethnicity	Age - Mean (SD): 37 (6.5). Gender (M:F): 88/15. Ethnicity: 60% Caucasian , 14% Hispanic, 20% African-American and 6% other
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (Adult ADHD Rating Scale (Mean (SD)) PBO=33.47 (10.39) versus MPH= 30.40 (9.78)). 2. Age: Adults 18-65 (18-60). 3. Previous treatment: Not stated / Unclear (Exclusion: were prescribed any psychotropic medication; Unclear if there was a history of pharmacological treatment for ADHD).
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Pharma + non-pharma - Stimulants + CBT. A 1-week placebo (PBO) lead-in phase, a 2-week close titration phase followed by 11 weeks at a stable close. All patients received two capsules twice a day, even when main-tained on PBO. Following the PBO lead-in phase, participants were randomized into either the MPH or PBO group. The dosing was initiated at 10 mg/day of standard formulation methylphenidate and increased up to 20 mg two times a day (40 mg/day). If tolerated, the sustained-release formulation replaced the standard formulation and was administered as two 20 mg doses (one in the morning, one in the after- noon). The dose was then increased to the maximal dose of 60 mg/day (40 mg in the morning and 20 mg in the afternoon), depending on patient tolerance of MPH. Patients who could not tolerate a close of at least 40 mg/day of MPH were discontinued off the medication but were continued in the trial. Also, 25 mg of ribollavin was added 10 each of the four prescribed capsules (approximately 100 mg/day) in an effort to track compliance. All participants attended weekly individual cognitive behavioral therapy (CBT). To ensure that all patients receive the same "close" of CBT, a structured relapse prevention manual was used . This manual was modified for use with individuals with individuals with ADHD.

Study	Levin 2007[37]
	Duration 14 weeks. Concurrent medication/care: Unclear (n=53) Intervention 2: Placebo/usual care. Placebo+CBT A 1-week placebo (PBO) lead-in phase, a 2-week close titration phase followed by 11 weeks at a stable close. All patients received two capsules twice a day, even when main-tained on PBO. Following the PBO lead-in phase, participants were randomized into either the MPH or PBO group. Folic acid in the form of a 1 mg tablet was added 10 all placebo capsules in an attempt to improve the double-blind. Also, 25 mg of ribollavin was added 10 each of the four prescribed capsules (approximately 100 mg/day) in an effort to track compliance. All participants attended weekly individual cognitive behavioral therapy (CBT). To ensure that all patients receive the same "close" of CBT, a structured relapse prevention manual was used . This manual was modified for use with individuals with individuals with ADHD . Duration 14 weeks. Concurrent medication/care: Unclear
Funding	Other (NIDA grants RO 1 DA 11755 and K02 00465. Dr. Lev in is a consultant for Eli Lily and Company, Shire Pharmaceuticals Group, AstraZeneca, Cephalon/ Alkermes and OrthoMcNeil Pharmaceutical Inc. Also she has research support from Eli Lily and Company, UCB Pharma Inc, Shire Pharmaceuticals Group, AstraZeneca and OrthoMcNeil Pharmaceutical Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CBT versus PLACEBO/USUAL CARE

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Adults over 18: Targeted Adult Attention Deficit Disorder Scale (TAADDS)

at 14 weeks PT; Group 1: 21/53, Group 2: 15/53; Comments: 30% reduction from baseline

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Demographics, baseline ADHD scores, baseline cocaine use, or the prevalence of co-morbid substance abuse or psychiatric disorders

; Blinding details: No caregiver; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Adults over 18: Adult ADHD Rating Scale (AARS)

Study	Levin 2007[37]
at 14 weeks PT; Group 1: 25/53, Group 2: 29/53; Comments: 30% reduction from baseline in the AARS Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Demographics, baseline ADHD scores, baseline cocaine use, or the prevalence of co-morbid substance abuse or psychiatric disorders ; Blinding details: No caregiver; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: CGI-I at <3 months - Actual outcome for Adults over 18: CGI ADHD improvement scale at 14 weeks PT; Group 1: 18/53, Group 2: 16/53; Comments: rated as much or very much improved on the CGI ADHD improvement scale Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Demographics, baseline ADHD scores, baseline cocaine use, or the prevalence of co-morbid substance abuse or psychiatric disorders ; Blinding details: No caregiver; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Li 2013[38]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)

Study	Li 2013[38]
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Intervention + follow up: 8-20 weeks + 6 month FU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): 10.6 (2.8). Gender (M:F): Define. Ethnicity: Not stated.
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (7-16). 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Pharma + non-pharma - Other. EEG feedback - All training performed on Autogenic A620 EEG feedback therapeutic apparatus. The 4-8 Hz 0 wave was suppressed while the 12-15 Hz SMR was strengthened. Instructions and game sequences were unified. Patients received the training 2 to 5 times a week and training sessions lasted 25 to 35 minutes. Methylphenidate - starting dose was 5-10mg once a day. The dose could be increased by 5 mg per week until the optimal dose was achieved. The maximum dose taken per day was not more than 60mg. Duration 8-20 weeks. Concurrent medication/care: Before receiving EEG treatment or non-feedback attention training patients had been treated with methylphenidate and the optimal therapeutic effects were obtained by titrating the dose of methylphenidate. At the end of training the minimum effective dose was used for maintenance therapy. (n=32) Intervention 2: Pharma + non-pharma - Other. Non-feedback attention training - All training performed on Autogenic A620 EEG feedback therapeutic apparatus. Threshold was set to non-feedback status. Instructions and game sequences were unified. Patients received the training 2 to 5 times a week and training sessions lasted 25 to 35 minutes. Methylphenidate - starting dose was 5-10mg once a day. The dose could be increased by 5 mg per week until the optimal dose was achieved. The maximum dose taken per day was not more than 60mg. Duration 8 - 20 weeks. Concurrent medication/care: Before receiving EEG treatment or non-feedback attention training patients had been treated with methylphenidate and the optimal therapeutic effects were obtained by titrating the dose of methylphenidate. At the end of training the minimum effective dose was used for maintenance

Study	Li 2013[38]
	therapy.
Funding	Academic or government funding (Dr Li Yang received research grant from Janssen Science Council of China.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDICATION AND EEG FEEDBACK versus MEDICATION + NON-FEEDBACK ATTENTION TRAINING

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: DSM-IV total score - parent at 8-20 weeks PT; Group 1: mean 38.6 (SD 7.8); n=32, Group 2: mean 41.2 (SD 9.9); n=32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome for Children and young people 5 to 18: DSM-IV total score - teacher at 8-20 weeks PT; Group 1: mean 37.9 (SD 8.7); n=32, Group 2: mean 41.8 (SD 11.1); n=32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A

Protocol outcome 2: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: DSM-IV total score - teacher at 6 months FU; Group 1: mean 35 (SD 7.4); n=31, Group 2: mean 43.7 (SD 9.8); n=29
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: N/A; Group 2 Number missing: 3, Reason: N/A
- Actual outcome for Children and young people 5 to 18: DSM-IV total score - parent at 6 months FU; Group 1: mean 37.9 (SD 6.5); n=31, Group 2: mean 44.9 (SD 8.5); n=29
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: N/A; Group 2 Number missing: 3, Reason: N/A

Protocol outcome 3: ADHD symptoms - Inattention at <3 months
- Actual outcome for Children and young people 5 to 18: DSM-IV ADHD attention deficit score - parent at 8-20 week PT; Group 1: mean 22.6 (SD 3.7); n=32, Group 2: mean 23.9 (SD 6); n=32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A
- Actual outcome for Children and young people 5 to 18: DSM-IV ADHD attention deficit score - teacher at 8-20 week PT; Group 1: mean 21.2 (SD 4.6); n=32, Group 2: mean 23.6 (SD 6.3); n=32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Li 2013[38]
- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: ADHD symptoms - Inattention at >3 months - Actual outcome for Children and young people 5 to 18: DSM-IV ADHD attention deficit score - teacher at 6 month FU; Group 1: mean 19.9 (SD 3.9); n=31, Group 2: mean 25.4 (SD 3.6); n=29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: N/A; Group 2 Number missing: 3, Reason: N/A - Actual outcome for Children and young people 5 to 18: DSM-IV ADHD attention deficit score - parent at 6 month FU; Group 1: mean 21.6 (SD 4.5); n=31, Group 2: mean 25.7 (SD 4.7); n=29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: N/A; Group 2 Number missing: 3, Reason: N/A Protocol outcome 5: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: DSM-IV hyperactivity/impulsivity score - parent at 8-20 weeks PT; Group 1: mean 16.6 (SD 4.7); n=32, Group 2: mean 17.3 (SD 6.3); n=32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome for Children and young people 5 to 18: DSM-IV hyperactivity/impulsivity score - teacher at 8-20 weeks PT; Group 1: mean 16.8 (SD 5.6); n=32, Group 2: mean 18.4 (SD 6.5); n=32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 6: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: DSM-IV hyperactivity/impulsivity score - teacher at 6 months FU; Group 1: mean 16.1 (SD 6.5); n=31, Group 2: mean 19.8 (SD 6.1); n=29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: N/A; Group 2 Number missing: 3, Reason: N/A - Actual outcome for Children and young people 5 to 18: DSM-IV hyperactivity/impulsivity score - parent at 6 months FU; Group 1: mean 16 (SD 4); n=31, Group 2: mean 19.2 (SD 6.1); n=29 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: N/A; Group 2 Number missing: 3, Reason: N/A	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Merrill 2016[41]
Study type	RCT (Patient randomised; Crossover: 2 weeks titration)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Unknown
Line of therapy	1st line
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	All participants met DSM-5 diagnostic criteria for ADHD.
Exclusion criteria	If they had an estimated Full-scale IQ below 80, had a previous diagnosis of Autism Spectrum disorder, were currently receiving psychotropic medications for conditions other than ADHD, had conditions that could be made worse by stimulant medication, or had documented intolerability or lack of response to stimulant medication.
Age, gender and ethnicity	Age - Mean (SD): 8 (1.70). Gender (M:F): 53 male, 22 female. Ethnicity: 89% White, 15% Black and 1% American Indian/Alaska Native.
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (Aged 5 - 12). 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Placebo/usual care. A wait list control group. Duration 8 weeks. Concurrent medication/care: None specified. (n=36) Intervention 2: Mixed medication - Non-specific medication. Children underwent a 2 week titration period and were randomized to receive 3 different doses of once daily, extended release MPH (Concerta 18, 27 and 36 mg, except for 10 children who received comparable doses of Focalin XR). The lowest dose that produced substantive or incremental efficacy with minimal side effects during the 2 week titration was administered during a subsequent medication crossover. Children received medication or placebo for 3 consecutive weeks, including weekends and the crossover condition for the final 3 weeks of the STP. Duration 8 weeks. Concurrent medication/care: All were receiving either BPT & DRC or on the wait list. (n=39) Intervention 3: Carer and family training problem - With involvement of person with ADHD.

Study	Merrill 2016[41]
	Homework-focused behavioral intervention. A behavioral treatment program based on Power's work developing the FSS and the Homework success program as well as general parent training content from the community parent education program. Homework focused sessions and general parent training skills. Families sit in small subgroups of 7 parents, watch videotaped vignettes of parenting errors, discuss parenting errors and alternative strategies. Parent subgroup leaders report back to the larger group after each discussion and BPT clinicians facilitate discussion. BPT and DRC consists of six 2hr group sessions in the evenings during the first 2 weeks of STP and one 30 min individual session was completed during subsequent 2 weeks. All children had a goal stating "completes homework with 80% accuracy". Duration 8 weeks. Concurrent medication/care: All children involved in a 3-week double blind placebo/medication crossover. (n=39) Intervention 4: Pharma + non-pharma - Mixed medication + carer/family +/- teacher training. The parent/family training intervention and medication intervention. Duration 8 weeks. Concurrent medication/care: None stated.
Funding	Academic or government funding (This research was conducted within a grant funded by the National Institute of Mental Health. Dr Pelham was also supported by grants from the institute of Education Sciences, the National Institute of Mental Health, the National Institute of Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse.)

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

Protocol outcome 1: Academic outcomes at <3 months
- Actual outcome for Children and young people 5 to 18: Math accuracy (%) at 8 weeks PT; Group 1: mean 87.75 (SD 7.49); n=36, Group 2: mean 83.85 (SD 8.79); n=36
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis
- Actual outcome for Children and young people 5 to 18: Reading/Language Arts (RLA) accuracy (%) at 8 weeks PT; Group 1: mean 86.14 (SD 10.14); n=36, Group 2: mean 82.76 (SD 11.35); n=36
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis

Study	Merrill 2016[41]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENT/FAMILY TRAINING versus NO TREATMENT. Protocol outcome 1: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: Math accuracy (%) at 8 weeks PT; Group 1: mean 91.89 (SD 5.42); n=39, Group 2: mean 83.85 (SD 8.79); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis - Actual outcome for Children and young people 5 to 18: Reading/Language Arts (RLA) accuracy (%) at 8 weeks PT; Group 1: mean 91.59 (SD 6.96); n=39, Group 2: mean 82.76 (SD 11.35); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENT/FAMILY TRAINING versus MEDICATION Protocol outcome 1: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: Maths accuracy (%) at 8 weeks PT; Group 1: mean 91.89 (SD 5.42); n=39, Group 2: mean 87.75 (SD 7.49); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis - Actual outcome for Children and young people 5 to 18: Reading/Language Arts (RLA) accuracy (%) at 8 weeks PT; Group 1: mean 91.59 (SD 6.96); n=39, Group 2: mean 86.14 (SD 10.14); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARENT/FAMILY TRAINING versus COMBINATION Protocol outcome 1: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: Maths accuracy (%) at 8 weeks PT; Group 1: mean 91.89 (SD 5.42); n=39, Group 2: mean 90.94 (SD 5.55); n=39	

Study	Merrill 2016[41]
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis - Actual outcome for Children and young people 5 to 18: Reading/Language Arts (RLA) accuracy (%) at 8 weeks PT; Group 1: mean 91.59 (SD 6.96); n=39, Group 2: mean 90.42 (SD 7.02); n=39 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus NO TREATMENT. Protocol outcome 1: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: Maths accuracy (%) at 8 weeks PT; Group 1: mean 90.94 (SD 5.55); n=39, Group 2: mean 83.85 (SD 8.79); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis - Actual outcome for Children and young people 5 to 18: Reading/Language Arts (RLA) accuracy (%) at 8 weeks PT; Group 1: mean 90.42 (SD 7.02); n=39, Group 2: mean 82.76 (SD 11.35); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus MEDICATION Protocol outcome 1: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: Maths accuracy (%) at 8 weeks PT; Group 1: mean 90.94 (SD 5.55); n=39, Group 2: mean 87.75 (SD 7.49); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis - Actual outcome for Children and young people 5 to 18: Reading/Language Arts (RLA) accuracy (%) at 8 weeks PT; Group 1: mean 90.42 (SD 7.02);	

Study	Merrill 2016[41]
n=39, Group 2: mean 86.14 (SD 10.14); n=36 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Blinding details: Medication group - double blinded; Group 1 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis; Group 2 Number missing: 0, Reason: Parent/family training group - 1 dropped out before analysis, Wait List group - 3 dropped out before analysis	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months

Study	Mohammadi 2014[43]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Iran; Setting:
Line of therapy	1st line
Duration of study	Intervention time: Not stated.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 6-12, diagnosis of ADHD based on Diagnostic and Statistical manual Disorders IV, confirmed by the clinic's psychiatrists as well as Conners Parent Rating scale (CPRS-48) which was applied by the researcher.
Exclusion criteria	Simultaneity of pervasive developmental disorders, mental retardation, major physical disease, records in drug abuse in subjects or parents, symptoms of psychosis in subjects or any need to be hospitalized.
Recruitment/selection of patients	Subjects were 6-12 year olds suffering from ADHD who were referred to Tehran's Children Psychotherapy Clinic in 2011 and qualified for research parameters.

Study	Mohammadi 2014[43]
Age, gender and ethnicity	Age - Mean (range): 6-12 years old. Gender (M:F): Not given. Ethnicity: Not stated.
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Pharma + non-pharma - Other. None given. Duration Unclear. Concurrent medication/care: N/A (n=25) Intervention 2: CNS stimulants - Methylphenidate. None given. Duration Unclear. Concurrent medication/care: N/A
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE + WORKING MEMORY TRAINING versus METHYLPHENIDATE Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Children and young people 5 to 18: Not specifically stated. CPRS-48. Parent rated. at Post Intervention; Group 1: mean 49.73 (SD 4.13); n=23, Group 2: mean 58.4 (SD 5.79); n=25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Montoya 2014[44]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=270)
Countries and setting	Conducted in Spain; Setting: outpatient

Study	Montoya 2014[44]
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinically confirmed diagnosis of ADHD (Diagnostic and Statistical Manual of Mental Disorders, Text Revision Fourth Edition [DSM-IV-TR] criteria)
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were children or adolescents aged 6–12 years with a clinically confirmed diagnosis of ADHD, an Attention Deficit Hyperactivity Disorder Rating Scale IV-Parent Version (ADHD-RS-IV Parent:Inv) score at least 1.5 standard deviations above the age norm for their diagnostic subtype, and a Clinical Global Impression-ADHD Severity (CGI-ADHD-S) score >4 at baseline; pharmacologically naïve and willing to commence on medication at the same time as the first planned psychoeducation session. Participating parents/guardians were required to be the primary caregiver and legal guardian of the patient.
Exclusion criteria	if pharmacologic treatment for ADHD was contraindicated for their children, or if either the parent/guardian or child was likely to start a structured psychoeducation program for ADHD outside of this trial. Parents/guardians were also excluded if their children had a history of bipolar disorder, psychosis, or autism spectrum disorder, or were in any way unsuitable to participate in the study.
Recruitment/selection of patients	Centers recruited patients sequentially over time into clusters and each cluster was then randomly assigned. No further details.
Age, gender and ethnicity	Age - Mean (SD): 9.1 (1.9). Gender (M:F): 195/75. Ethnicity: no information
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (6-12 years). 3. Previous treatment: Naive (Patients were required to be pharmacologically naïve).
Extra comments	. cluster randomised
Indirectness of population	No indirectness
Interventions	(n=144) Intervention 1: Pharma + non-pharma - Mixed medication + coaching/mentoring/psychoeducation/counselling. medication: not specified, Medication was administered at the discretion of the attending physician in accordance with the ADHD guidelines produced by the National Institute for Health and Care Excellence. Parental psychoeducation sessions lasted for 90 minutes and were given once weekly for the first 4 weeks followed by a fifth session after a 5-week break. They consisted of lectures, small-group and large-group discussions, shared learning from previous sessions, and homework. Sessions content include provision of information on ADHD in general, pharmacologic management, and behavior management. Duration 12 months (FU). Concurrent medication/care: no information

Study	Montoya 2014[44]
	(n=126) Intervention 2: Mixed medication - Non-specific medication. Medication was administered at the discretion of the attending physician in accordance with the ADHD guidelines produced by the National Institute for Health and Care Excellence. Duration no information. Concurrent medication/care: no information Comments: most frequently prescribed ADHD agents at baseline and during the study were long-acting methylphenidate (Concerta) Medikinet, atomoxetine (Strattera), and short-acting methylphenidate (Rubifen)
Funding	Funding not stated (two authors are full-time employees of and shareholders in Eli Lilly; other authors also related to industry; editorial support was funded by Eli Lilly)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + PARENT PSYCHOEDUCATION versus MIXED MEDICATION

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: change score ADHD-RS (FU) at 12 months; MD; -3.362 (95%CI -6.335 to -0.389, Comments: comparison of the change from baseline in ADHD-RS-IV Parent score; MD=an estimated adjusted mean (least square mean [LSM]); these results favor psychoeducation
);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline ADHD-RS -IV Parent:Inv score, mean (SD) combined: 36.2 (9.0), medication alone: 39.5 (9.0).
Baseline CGI-ADHD-S score, mean (SD), combined: 5.0 (0.9), medication alone: 5.0 (1.0).

; Group 1 Number missing: 28, Reason: n=10 parent decision, n=5 sponsor decision, n=8 lost to follow up, n=2 adverse event, n=1 pharmacologic withdrawal, n=1 decision patient; Group 2 Number missing: 34, Reason: n=12 parent decision, n=7 adverse event, n=3 lost to follow up, n=3 physician decision, n=3 protocol violation, n=3 unknown, n=1 pharmacologic withdrawal

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: change score ADHD-RS inattention subscore (FU) at 12 months; MD; -1.863 (95%CI -3.48 to -0.247, Comments: comparison of the change from baseline in ADHD-RS-IV inattention subscore, Parent score; MD=an estimated adjusted mean (least square mean [LSM]); these results favor psychoeducation
);
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline ADHD-RS -IV Parent:Inv score,

Study	Montoya 2014[44]
	mean (SD) combined: 36.2 (9.0), medication alone: 39.5 (9.0). Baseline CGI-ADHD-S score, mean (SD), combined: 5.0 (0.9), medication alone: 5.0 (1.0). ; Group 1 Number missing: 28, Reason: n=10 parent decision, n=5 sponsor decision, n=8 lost to follow up, n=2 adverse event, n=1 pharmacologic withdrawal, n=1 decision patient; Group 2 Number missing: 34, Reason: n=12 parent decision, n=7 adverse event, n=3 lost to follow up, n=3 physician decision, n=3 protocol violation, n=3 unknown, n=1 pharmacologic withdrawal Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Children and young people 5 to 18: change score ADHD-RS hyperactivity/impulsivity subscore (FU) at 12 months; MD; -1.498 (95%CI -3.125 to 0.128, Comments: comparison of the change from baseline in ADHD-RS-IV, subscale hyperactivity/impulsivity Parent score; MD=an estimated adjusted mean (least square mean [LSM]);); Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline ADHD-RS -IV Parent:Inv score, mean (SD) combined: 36.2 (9.0), medication alone: 39.5 (9.0). Baseline CGI-ADHD-S score, mean (SD), combined: 5.0 (0.9), medication alone: 5.0 (1.0). ; Group 1 Number missing: 28, Reason: n=10 parent decision, n=5 sponsor decision, n=8 lost to follow up, n=2 adverse event, n=1 pharmacologic withdrawal, n=1 decision patient; Group 2 Number missing: 34, Reason: n=12 parent decision, n=7 adverse event, n=3 lost to follow up, n=3 physician decision, n=3 protocol violation, n=3 unknown, n=1 pharmacologic withdrawal
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Hyperactivity at <3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Philipsen 2015[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=433)
Countries and setting	Conducted in Germany; Setting: University hospital
Line of therapy	1st line

Study	Philipsen 2015[49]
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: the Wender Utah Rating Scale (WURS-k; in German), the ADHD diagnostic checklist (ADHD-DC; in German), and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (in German).
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	□ Male and female □ Subjects must speak German fluently □ Aged 18–60 years inclusive □ Diagnosis of ADHD according to the DSM-IV criteria □ A score of greater than 30 on the short version of the Wender Utah Rating Scale □ Chronic course of ADHD symptoms from childhood to adulthood □ Subjects provided written informed consent in accordance with international guidelines and local legislation □ Unobtrusive physical examination (including blood pressure/heart rate) without serious or uncontrolled Findings □ Lab results without clinically relevant findings (e.g., blood count, renal retention data, tests of liver function, thyroid parameters). EKG and EEG without pathologically relevant results □ The screening has been fully completed. Laboratory results are not more than 6 weeks old and (if applicable) pregnancy test is not more than 2 weeks before the time of randomization. □ It is possible to conduct the baseline assessment within 7 days of randomization and to begin therapy within 14 days
Exclusion criteria	□ IQ <85 according to a score of <17 on the Multiple-Choice Vocabulary Intelligence Test (MWT-B, German version1) □ Schizophrenia, bipolar affective disorder, borderline personality disorder, antisocial personality disorder, suicidality or self-harm, autism, motor tics, Tourette Syndrome □ Substance abuse or dependence in the previous 6 months before the screening. Episodic consumption is not an exclusion criterion. A positive drug test during screening □ Neurological disorders, seizures, pathological EEG results (lateral differences, lesion, epileptiform potentials), glaucoma, diabetes mellitus, fasting blood glucose level >110 mg/dl, hyperlipidemia, uncontrolled arterial hypertension (according to the guidelines of the German Hypertension Society), angina pectoris, known arterial occlusive disease or another manifestation of vascular disease, known tachycardic arrhythmias □ History of stroke □ Known enlarged prostate □ Current eating disorder (bulimia nervosa, anorexia nervosa, Body Mass Index <19) □ Participation in a clinical trial within 3 months before the beginning of the study or concurrent participation in another clinical trial □ Medication with stimulants or ADHD-specific psychotherapy within the previous 6 months before the beginning of the study □ Known hypersensitivity to methylphenidate, other sympathomimetic drugs, or any other excipients □

Study	Philipsen 2015[49]
	Unwillingness or inability to comply with the requirements of the study protocol Patient is unable to understand the nature, significance, and scope of the study Current or planned pregnancy, without the use of defined methods of contraception; lactation; positive pregnancy test during screening Use of another psychopharmacological medication in addition to randomized treatment before the start of treatment or during study participation (definition of non-approved medication and the required timing of weaning before treatment) Regular participation in other outpatient psychotherapy during study participation
Recruitment/selection of patients	University hospital
Age, gender and ethnicity	Age - Mean (SD): 35 (10.26). Gender (M:F): 210/223. Ethnicity: White range 97.1-100%
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (ADHD Index (CAARS): Mean 20.6). 2. Age: Adults 18-65 3. Previous treatment: (Exclusion criteria: Medication with stimulants or ADHD-specific psychotherapy within the previous 6 months before the beginning of the study).
Indirectness of population	No indirectness
Interventions	(n=103) Intervention 1: Pharma + non-pharma - Stimulants + CBT. Following randomization and baseline assessment, participants received methylphenidate hydrochloride (sustained release; initial dosage of 10 mg/d; titration with 10 mg/week over 6 weeks up to 60 mg/d; individual dosage to a maximum daily dosage of 1.3 mg/kg of body weight) or placebo. Medication adherence was assessed by pill count. Group psychotherapy was conducted according to the manual of Hesslinger and co-workers1 who developed a structured program for adult patients suffering from ADHD. The program is based on the principles of dialectical-behavioral therapy of borderline personality disorder (BPD) and cognitive behavioral treatment because ADHD and BPD share several clinical features (e.g. problems in emotion regulation and impulse control, low self-esteem, disturbed interpersonal relationships. The efficacy and feasibility of the program were demonstrated for adult outpatients in an open trial and randomized controlled trial. In the first 12 weekly sessions, the following themes were covered: Session 1 (introduction) Session 2 (mindfulness) Session 3 (mindfulness II) Session 4 (chaos and control) Session 5 (functional analysis I) Session 6 (functional analysis II) Session 7 (emotion regulation) Session 8 (depression/medication in ADHD) Session 9 (impulse control) Session 10 (stress management) Session 11 (dependency/abuse) Session 12 (ADHD in relationships/self-respect Sessions 13 to 21 took place every four weeks. Focus was on the consolidation of skills. Themes of the sessions were defined in cooperation with the patient group. Repetition of the modules' mindfulness, chaos and control, functional analysis, emotion regulation and stress management was mandatory. Session 22 (retrospect and outlook): Discussing attained individual goals and helpful strategies, planning strategies for achieving remaining goals, discussing possibilities on how to keep contact with the other group members.

Study	Philipsen 2015[49]
	Group psychotherapy sessions had a common structure: Duration: 2 x 50 minutes, interrupted by a brake of 20 minutes; 1st part: greeting, mindfulness exercise, discussion of accomplished therapeutic tasks (referring to the skills protocols), consolidation of the theme of the last week; 2nd part: mindfulness exercise, introduction and discussion of the new theme/skill, assignment of therapeutic tasks, wind down, rating of the session. . Duration 52 weeks. Concurrent medication/care: unclear (n=106) Intervention 2: Cognitive behavioural therapies - CBT. Placebo and cognitive behavioral group psychotherapy (GPT, see description in the Stimulant+CBT intervention arm) . Duration 52 weeks. Concurrent medication/care: Unclear (n=110) Intervention 3: Pharma + non-pharma - Stimulants + coaching/mentoring/psychoeducation/counselling. Methylphenidate titrated over 6 weeks and continued for 1 year + clinical management (non-specific supportive therapy) delivered in 12 weekly sessions and then once monthly for the rest of the year. Duration 52 weeks. Concurrent medication/care: Usual care (n=107) Intervention 4: Non-specific supportive non-pharmacological therapy - NSSNPT. Clinical management (as per description for stimulants + NSST). Duration 52 weeks. Concurrent medication/care: Usual care
Funding	-- (Grants 01GV0605 and 01GV0606 from the German Federal Ministry of Education and Research. MEDICE Arzneimittel Puetter GmbH and Co KG provided the trial medication (Medikinet retard licensed as Medikinet adult and matching placebo).

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

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Adults over 18: Observer-Rated CAARS Score total

at 52 weeks PT; Group 1: mean 14.9 (SD 6.65); n=103, Group 2: mean 16.4 (SD 6.14); n=106; Observer-Rated CAARS Score ADHD index 0-36 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Philipsen 2015[49]
Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data - Actual outcome for Adults over 18: Self-Rated CAARS Score total at 52 weeks PT; Group 1: mean 15.3 (SD 6.14); n=103, Group 2: mean 16.9 (SD 6.78); n=106; Self-Rated CAARS Score total 0-36 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Inattention memory problems at 52 weeks PT; Group 1: mean 15 (SD 6.14); n=103, Group 2: mean 16 (SD 6.75); n=106; Observer-Rated CAARS Score Inattention memory problems 0-36 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Hyperactivity/restlessness at 52 weeks PT; Group 1: mean 13 (SD 6.14); n=103, Group 2: mean 14.9 (SD 7.16); n=106; Observer-Rated CAARS Score Hyperactivity/restlessness 0-36 Top=High is poor outcome	

Study	Philipsen 2015[49]
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 4: Emotional dysregulation at >3 months - Actual outcome for Adults over 18: Self-Rated BDI at 52 weeks PT; Group 1: mean 8.9 (SD 7.16); n=103, Group 2: mean 9.4 (SD 7.16); n=106; BDI 0-63 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CBT versus STIMULANTS + NSST Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score total at 52 weeks PT; Group 1: mean 14.9 (SD 6.65); n=103, Group 2: mean 14.6 (SD 6.35); n=110 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data - Actual outcome for Adults over 18: Self-Rated CAARS Score total at 52 weeks PT; Group 1: mean 15.3 (SD 6.14); n=103, Group 2: mean 15.1 (SD 6.88); n=106 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment.	

Study	Philipsen 2015[49]
	; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Inattention memory problems at 52 weeks PT; Group 1: mean 15 (SD 6.14); n=103, Group 2: mean 15.2 (SD 6.23); n=110 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Hyperactivity/restlessness at 52 weeks PT; Group 1: mean 13 (SD 6.14); n=103, Group 2: mean 13.3 (SD 6.23); n=110 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 4: Emotional dysregulation at >3 months - Actual outcome for Adults over 18: Self-Rated BDI at 52 weeks PT; Group 1: mean 8.9 (SD 7.16); n=103, Group 2: mean 9.6 (SD 7.4); n=110 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment.

Study	Philipsen 2015[49]

; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CBT versus NSST

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Adults over 18: Observer-Rated CAARS Score total

at 52 weeks PT; Group 1: mean 14.9 (SD 6.65); n=103, Group 2: mean 17.5 (SD 7.16); n=107
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment.

; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data
- Actual outcome for Adults over 18: Self-Rated CAARS Score total

at 52 weeks PT; Group 1: mean 15.3 (SD 6.14); n=103, Group 2: mean 18 (SD 6.65); n=107
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment.

; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data

Protocol outcome 2: ADHD symptoms - Inattention at <3 months
- Actual outcome for Adults over 18: Observer-Rated CAARS Score Inattention memory problems

at 52 weeks PT; Group 1: mean 15 (SD 6.14); n=103, Group 2: mean 17.5 (SD 7.16); n=107
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment.

; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data

Study	Philipsen 2015[49]
Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Hyperactivity/restlessness at 52 weeks PT; Group 1: mean 13 (SD 6.14); n=103, Group 2: mean 15.2 (SD 7.16); n=107 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 4: Emotional dysregulation at >3 months - Actual outcome for Adults over 18: Self-Rated BDI at 52 weeks PT; Group 1: mean 8.9 (SD 7.16); n=103, Group 2: mean 10.1 (SD 8.19); n=107 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + NSST versus CBT Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score total at 52 weeks PT; Group 1: mean 14.6 (SD 6.35); n=110, Group 2: mean 16.4 (SD 6.14); n=106 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data	

Study	Philipsen 2015[49]
- Actual outcome for Adults over 18: Self-Rated CAARS Score total at 52 weeks PT; Group 1: mean 15.1 (SD 6.88); n=110, Group 2: mean 16.9 (SD 6.78); n=106 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 2: ADHD symptoms - Inattention at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Inattention memory problems at 52 weeks PT; Group 1: mean 15.2 (SD 6.23); n=110, Group 2: mean 16 (SD 6.75); n=106 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: Observer-Rated CAARS Score Hyperactivity/restlessness at 52 weeks PT; Group 1: mean 13.3 (SD 6.23); n=110, Group 2: mean 14.9 (SD 7.16); n=106 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Family life, Employment, ADHD-type, IQ , Comorbid disorders, previous treatment. ; Group 1 Number missing: 4, Reason: No baseline data; Group 2 Number missing: 3, Reason: No baseline data Protocol outcome 4: Emotional dysregulation at >3 months	

Study	Philipsen 2015[49]
- Actual outcome for Adults over 18: Self-Rated BDI at 52 weeks PT; Group 1: mean 9.6 (SD 7.4); n=110, Group 2: mean 9.4 (SD 7.16); n=106 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Riggs 2011[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=303)
Countries and setting	Conducted in USA; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E)
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Criteria for study participation included meeting Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) diagnostic criteria for current ADHD and at least one nontobacco SUD.
Exclusion criteria	Current or past psychotic disorder, bipolar disorder, suicide risk, opiate dependence, methamphetamine abuse or dependence, cardiac illness or serious medical illness, pregnancy, past month use of psychotropic medications or participation in other substance or mental health treatment
Recruitment/selection of patients	Referral sources (e.g. juvenile justice, social services agencies), primary care and mental health clinics, schools, and media advertising at 11 community-based substance treatment programs in the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN).

Study	Riggs 2011[50]
Age, gender and ethnicity	Age - Mean (SD): 16.5 (1.3). Gender (M:F): 239/64. Ethnicity: Caucasian, 61.7%; African American, 23.2%; other, 15.1%. Ethnicity: Hispanic, 15.2%.
Further population details	1. ADHD symptom severity: Majority moderate (ADHD Rating Scale score, mean (SD) 38.7 (8.9)). 2. Age: Young people 12-17 (aged 13-18 years). 3. Previous treatment: Not stated / Unclear (Exclusion: past month use of psychotropic medications).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=151) Intervention 1: Pharma + non-pharma - Stimulants + CBT. Medication—Participants were started on a 18 mg dose of OROS-MPH/matching placebo and titrated to a single fixed morning dose of 72mg (or highest dose tolerated) during the first two study weeks, post-randomization. Cognitive Behavioral Therapy (CBT)—Participants in both medication groups received manual-standardized, individual CBT using motivational enhancement approaches throughout the 16 week medication trial. The efficacy and feasibility of training and implementation of the manual-driven CBT used in this study has been demonstrated in previous studies and cognitive behavioral principles have been widely adopted and are used in most existing community-based substance treatment programs. Master's level CBT therapists were trained and certified by the study's national trainer, who was herself trained and certified as both therapist and trainer by the developer of the manual. Of 147 sessions rated, 138 (94%) were rated as adherent. . Duration 16 weeks. Concurrent medication/care: Not reported (n=152) Intervention 2: Cognitive behavioural therapies - CBT. Placebo + CBT (see active medication arm). Duration 16 weeks. Concurrent medication/care: Not reported
Funding	Equipment / drugs provided by industry (National Institute on Drug Abuse (NIDA): U10 DA13716 (PDR, RDD, SMG, CK, MM, ML, EW); U10 DA13732 (PDR, TW, RDD, SMG, CK, MM, ML, EW); U10 DA15831 (GLB, WBJ); U10 DA13727 (LH, BWH); U10 DA13720 (CH, MAV); U10 DA20024 (KTR, LT); U10 DA13035 (EVN, MCA); K24 DA022412 (EVN); U10 DA13043 (CRM, GEW); U10 DA13034 (GS, MF); K12 DA000357 (GS); U10 DA20036 (MEK). Drug and matching placebo were provided by Ortho McNeil Janssen Scientific Affairs, LLC.)

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

Protocol outcome 1: ADHD symptoms (total) at <3 months

Study	Riggs 2011[50]
- Actual outcome for Children and young people 5 to 18: ADHD-RS (clinician) at 16 weeks (PT); Group 1: mean 17 (SD 7.20992); n=151, Group 2: mean 16.4 (SD 7.39101); n=152; clinician-administered DSM-IV ADHD Rating Scale (ADHD-RS; adolescent informant) 0-68 Top=High is poor outcome Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Ethnicity, ADHD-type and severity , Comorbid dependence, depressive and conduct disorders, ; Blinding details: no caregiver; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Safren 2005[51]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in USA; Setting: Not stated
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 15 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Met DSM-IV criteria for ADHD, stable medications for ADHD for 2 months (responding but still symptoms), aged 18 to 65,
Exclusion criteria	Variety of moderate to severe mental health disorders, previous use of CBT, IQ <90

Study	Safren 2005[51]
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 45.5 (10.6). Gender (M:F): 14:17. Ethnicity:
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 3. Previous treatment: Previously on drugs, mixed
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Pharma + non-pharma - Mixed medication + CBT. Continued previous non-specific ADHD medication + CBT. CBT delivered by psychologists, 4 sessions focused on psychoeducation, 3 sessions focused on learning skills to reduce distractability, remaining sessions aimed at cognitive restructuring. Optional additional modules on procrastination, anger management, communication skills. Duration 15 weeks. Concurrent medication/care: Not stated (n=15) Intervention 2: Mixed medication - Non-specific medication. Continued previous psychopharmacology, no other information provided. Duration 15 weeks. Concurrent medication/care: Nil stated
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + CBT versus NON-SPECIFIC MEDICATION

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Adults over 18: ADHD symptoms total, observer rated, ADHD-RS, 0-54, high is poor, FV, PT, >3 months at 15 weeks; Group 1: mean 15.19 (SD 7.12); n=16, Group 2: mean 20.8 (SD 10.84); n=15
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Adults over 18: ADHD symptoms total, self-rated, ADHD-RS, 0-54, high is poor, FV, PT, >3 months at 15 weeks; Group 1: mean 14.75 (SD 8.65); n=16, Group 2: mean 23.87 (SD 9.92); n=15
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: CGI-I at >3 months
- Actual outcome for Adults over 18: Responders, as defined by two point change in CGI-S to define responders at 15 weeks; Group 1: 9/16, Group 2: 2/15
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Study	Safren 2005[51]
Protocol outcome 3: Emotional dysregulation at >3 months - Actual outcome for Adults over 18: Hamilton depression, observer rated, 0-53, high is poor, FV, PT, >3 months at 15 weeks; Group 1: mean 4.44 (SD 2.7); n=16, Group 2: mean 10 (SD 7.78); n=15 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Safren 2010[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=86)
Countries and setting	Conducted in USA; Setting: Clinic
Line of therapy	1st line
Duration of study	Intervention + follow up: 67 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Structured Clinical Interview supplemented by questions from the Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiologic Version
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	1) principal diagnosis of ADHD (with childhood onset) and a Clinical Global Impression scale score for severity of 3 (mildly ill) or greater, (2) between the ages of 18 and 65 years, (3) able to provide informed consent and comply with study procedures, and (4) stabilized on psychotropic medications.
Exclusion criteria	1) moderate to severe major depression, clinically significant (i.e., Clinical Global Impression scale score for severity>4) panic disorder, organic mental disorders, psychotic spectrum disorders, bipolar disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder, (2) active suicidality, (3) history of cognitive behavioral therapy, and (4) antisocial personality disorder or a learning disability that would interfere with treatment.

Study	Safren 2010[52]
Recruitment/selection of patients	Patients were seen at Massachusetts General Hospital after being recruited through clinics affiliated with the hospital, local radio advertisements, advertisements posted throughout the hospital, as well as through referrals from other mental health professionals.
Age, gender and ethnicity	Age - Mean (SD): 43.2 (11.3). Gender (M:F): 48/38. Ethnicity: White N=78; Black N=5; Asian N=1; Middle Eastern N=1; Other N=1
Further population details	1. ADHD symptom severity: Mixed population (Clinical Global Impression scale score for severity of 3 (mildly ill) or greater). 2. Age: Adults 18-65 (18-65 years). 3. Previous treatment: Previously on drugs, not responsive
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Pharma + non-pharma - Mixed medication + CBT. Cognitive behavioral therapy for ADHD was delivered consistent with our manuals. It consisted of 3 core modules and 2 optional modules. The first module (4 sessions) focused on psycho-education about ADHD and training in organizing and planning (use of calendar and task list system), including problem-solving training (generating alternatives and picking the best solution, breaking down overwhelming tasks into steps). The second module (2 sessions) involved learning skills to reduce distractibility, such as techniques to time the length of one's attention span, and, when doing a task, write down distractions versus acting on them. The third module (3 sessions) was cognitive restructuring, which involved learning to think more adaptively in situations that cause distress. Optional modules were one session of application of skills to procrastination and one session including the patient's family member for support. Patients for whom the optional sessions were not relevant had booster sessions on prior material. The final session was focused on review and relapse prevention. . Duration 15 weeks. Concurrent medication/care: Patients were taking medications but still reporting clinically significant symptoms any medication prescribed by a psychiatrist for ADHD was permitted. If the medicines were not prescribed by a psychiatrist and were not typically used for ADHD, patients had a consultation with a study psychiatrist, were referred back to their prescribing physician, and could enter the study after 2 months of taking the new regimen. Groups were not stratified by medication type or dose. (n=43) Intervention 2: Pharma + non-pharma - Other. Relaxation with educational support (which is an attention-matched comparison). Patients in the relaxation condition received training in progressive muscle relaxation and other relaxation techniques as applied to ADHD symptoms, as well as education about ADHD and supportive psychotherapy. The first module involved psychoeducation (1 session). The second module trained patients in progressive muscle relaxation (6 sessions). The third module involved training in application of relaxation to ADHD symptoms (4 sessions). The final session involved review and planning for continued use of these skills (i.e., when feeling distracted or overwhelmed, use cued relaxation to calm down and decide what to do next)

Study	Safren 2010[52]
	. Duration 15 weeks. Concurrent medication/care: Patients were taking medications but still reporting clinically significant symptoms any medication prescribed by a psychiatrist for ADHD was permitted. If the medicines were not prescribed by a psychiatrist and were not typically used for ADHD, patients had a consultation with a study psychiatrist, were referred back to their prescribing physician, and could enter the study after 2 months of taking the new regimen. Groups were not stratified by medication type or dose.
Funding	Academic or government funding (National Institutes of Health grant 5R01MH69812)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + CBT versus MEDICATION AND RELAXATION WITH EDUCATIONAL SUPPORT

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Adults over 18: ADHD Rating Scale-IV (Dupaul) self-report
at 15 weeks PT; Group 1: mean 14.46 (SD 8.46); n=41, Group 2: mean 19.19 (SD 9.71); n=37
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Race, taking medication and type.
; Group 1 Number missing: 2, Reason: did not fill in post and follow-up tests; Group 2 Number missing: 5, Reason: did not fill in post and follow-up tests

Protocol outcome 2: ADHD symptoms (total) at >3 months
- Actual outcome for Adults over 18: ADHD Rating Scale-IV (Dupaul) self-report
at 67 weeks FU; Group 1: mean 13.39 (SD 8.49); n=38, Group 2: mean 16.97 (SD 1.72); n=32
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Race, taking medication and type.
; Group 1 Number missing: 5, Reason: did not fill in post and follow-up tests; Group 2 Number missing: 11, Reason: did not fill in post and follow-up tests

Protocol outcome 3: CGI-I at <3 months
- Actual outcome for Adults over 18: Clinical Global Impression scale
at 15 weeks PT; Group 1: 22/41, Group 2: 9/37; Comments: There was a greater proportion of responders in the cognitive behavioral therapy condition compared with the relaxation condition, using criteria from both the Clinical Global Impression scale (53% versus 23%; OR, 3.80 [95% CI, 1.50 to 9.59]; P=.01)

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education, Ethnicity, Race, taking medication and type.

Study	Safren 2010[52]
; Group 1 Number missing: 2, Reason: did not fill in post and follow-up tests; Group 2 Number missing: 5, Reason: did not fill in post and follow-up tests	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	So 2008[54]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Hong Kong (China); Setting: outpatient
Line of therapy	1st line
Duration of study	Intervention + follow up: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ADHD (combined type) according to DSM-IV
Stratum	Children and young people 5 to 18:
Subgroup analysis within study	Not applicable:
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	sample of consecutive referrals with ADHD symptoms to community child psychiatric clinic
Age, gender and ethnicity	Age - Mean (SD): 8.0 (0.9). Gender (M:F): Define. Ethnicity: Chinese
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (-). 2. Age: Children 6-12 (between 7 and 9.9 years). 3. Previous treatment: Naive (no past exposure to methylphenidate).
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Pharma + non-pharma - Stimulants + carer/family +/- teacher training. methylphenidate: immediate-release; initiated at dose of 5 mg once or twice daily and increased up to max 60 mg/day (doses raised with 5-10 mg until balance of improvement and minimal side effects). behavioral therapy: classroom programme for ADHD children and parents. 24 weekly sessions during 6 months in group format. 3 parts: 1. direct contingency management in laboratory classroom,2. skills training

Study	So 2008[54]
	for ADHD children (each session minimal 100 minutes), 3. parent training (each session minimal 90 minutes). 1 trainer and 2-3 assistants for a group of 8-9 ADHD children 1+2: by psychiatric nurse, clinical teacher and occupational therapist, supervised by clinical psychologist 3: by clinical psychologist (author study) laboratory classroom: a system of token economy, 6 rules prominently displayed in classroom (including work quietly, raise hands to speak or ask question, remain in assigned seat). children started in group with 180 tokens. Concurrently, individual target behaviours were identified. parents training: implementation of contingency management techniques based on social learning principles. Duration 6 months. Concurrent medication/care: no (n=41) Intervention 2: CNS stimulants - Methylphenidate. methylphenidate: immediate-release methylphenidate, Ritalin ; initiated at dose of 5 mg once or twice daily and increased up to max 60 mg/day (doses raised with 5-10 mg until balance of improvement and minimal side effects). Duration 6 months. Concurrent medication/care: no Comments: after the treatment phase, behavioral therapy (intervention group) was offered to patients in group methylphenidate alone
Funding	Academic or government funding (Quality Education Fund, HONG Kong SAR Government)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CARER/FAMILY versus METHYLPHENIDATE

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: SWAN inattention and hyperactivity subscale (PT) at 6 months; Group 1: mean 0.53 - (SD 0.77); n=45, Group 2: mean 0.94 - (SD 0.71); n=31; Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors ratings Scale - SWAN, ADHD inattention and hyperactivity / impulsivity subscale unclear Top=High is good outcome; Comments: SWAN: per item from -3 to +3, where 0 (zero) is normal and based upon the population average. no information about range for ADHD symptoms score
Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: combined: 60% ODD as comorbidity methylphenidate: 39% ODD as comorbidity; Group 1 Number missing: 3, Reason: n=3 dropped out; Group 2 Number missing: 13, Reason: n=3 not agreed to receive methylphenidate only, n=10 dropped out
- Actual outcome for Children and young people 5 to 18: SWAN inattention and hyperactivity subscale (FU 6 mo) at 12 months; Group 1: mean 0.58 - (SD 0.52); n=44, Group 2: mean 0.71 - (SD 0.59); n=31; Comments: SWAN: per item from -3 to +3, where 0 (zero) is normal and based upon the population average. no information about range for ADHD symptoms score
Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: combined: 60% ODD as comorbidity

Study	So 2008[54]
	methylphenidate: 39% ODD as comorbidity; Group 1 Number missing: 1, Reason: n=1 did not attend assessment; Group 2 Number missing: 17, Reason: n=3 not agreed to receive methylphenidate only, n=10 dropped out; n=4 excluded because they attended behavioral therapy at follow up - Actual outcome for Children and young people 5 to 18: SWAN inattention and hyperactivity subscale (FU 12 mo) at 18 months; Group 1: mean 0.6 - (SD 0.63); n=42, Group 2: mean 0.56 - (SD 0.57); n=16; Comments: SWAN: per item from -3 to +3, where 0 (zero) is normal and based upon the population average. no information about range for ADHD symptoms score Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: combined: 60% ODD as comorbidity methylphenidate: 39% ODD as comorbidity; Group 1 Number missing: 3, Reason: n=1 did not attend assessment FU 6 months, n= 2 did not attend assessment FU 12 months; Group 2 Number missing: 25, Reason: n=3 not agreed to receive methylphenidate only, n=10 dropped out; n=4 excluded because they attended behavioral therapy at FU 6 months, n=3 attended behavioral therapy at FU 12 months, n=5 did not attend assessment FU 12 months - Actual outcome for Children and young people 5 to 18: SWAN symptom composite score (FU 12 mo) at 18 months; Group 1: mean 0.55 - (SD 0.64); n=42, Group 2: mean 0.64 - (SD 0.47); n=16; SWAN rating scale, unclear Top=High is good outcome; Comments: SWAN: per item from -3 to +3, where 0 (zero) is normal and based upon the population average. no information reported about range for symptom composite score Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: combined: 60% ODD as comorbidity methylphenidate: 39% ODD as comorbidity; Group 1 Number missing: 3, Reason: n=1 did not attend assessment FU 6 months, n= 2 did not attend assessment FU 12 months; Group 2 Number missing: 25, Reason: n=3 not agreed to receive methylphenidate only, n=10 dropped out; n=4 excluded because they attended behavioral therapy at FU 6 months, n=3 attended behavioral therapy at FU 12 months, n=5 did not attend assessment FU 12 months - Actual outcome for Children and young people 5 to 18: SWAN symptom composite score (PT) at 6 months; Group 1: mean 0.53 - (SD 0.71); n=45, Group 2: mean 0.97 - (SD 0.67); n=31; Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors ratings Scale - symptom composite score unclear Top=High is good outcome; Comments: SWAN: per item from -3 to +3, where 0 (zero) is normal and based upon the population average. no information about range for symptom composite score Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: combined: 60% ODD as comorbidity methylphenidate: 39% ODD as comorbidity; Group 1 Number missing: 3, Reason: n=3 dropped out; Group 2 Number missing: 13, Reason: n=3 not agreed to receive methylphenidate only, n=10 dropped out - Actual outcome for Children and young people 5 to 18: SWAN symptom composite score (FU 6 mo) at 12 months; Group 1: mean 0.54 - (SD 0.56); n=44, Group 2: mean 0.68 - (SD 0.57); n=24; Comments: SWAN: per item from -3 to +3, where 0 (zero) is normal and based upon the population average. no information about range for symptom composite score Risk of bias: All domain - --, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: combined: 60% ODD as comorbidity methylphenidate: 39% ODD as comorbidity; Group 1 Number missing: 1, Reason: n=1 not attended assessment; Group 2 Number missing: 17, Reason:

Study	So 2008[54]
n=3 not agreed to receive methylphenidate only, n=10 dropped out (during treatment), n=4 attended behavioral therapy during follow up,	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Sprich 2016[55]
Study type	RCT (Patient randomised; Crossover: no)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in USA; Setting: outpatient clinic
Line of therapy	2nd line
Duration of study	Intervention time: 4 weeks (PT)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Principal diagnosis of ADHD and psychiatric comorbidity was confirmed by the Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiologic Version (Orvaschel, 1985) in separate interviews with the adolescent and parent.
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	adolescents ages 14–18, with a principal diagnosis of ADHD, with a Clinical Global Impression Severity Rating (CGI) of 3 (moderate severity) or greater at baseline, and on a stable dose (defined as no change in dose for at least 2 months) of an FDA-approved medication.
Exclusion criteria	severe comorbid disorders that would interfere with participation, active suicidality, conduct disorder, active substance abuse or dependence (<3 months remission), organic mental disorder, mental retardation, pervasive developmental disorder, or a history of CBT for ADHD.
Recruitment/selection of patients	recruited from the Pediatric Psychopharmacology Service, the Child Psychiatry Clinic, and the Pediatric Clinics at Massachusetts General Hospital. Recruitment strategies included letters to doctors, IRB-approved

Study	Sprich 2016[55]
	flyers, and advertising via radio and Facebook.
Age, gender and ethnicity	Age - Mean (SD): 15.13 (1.06). Gender (M:F): 36/10. Ethnicity: n=4 Hispanic or Latino, n=42 not Hispanic or Latino
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Young people 12-17 (14-18). 3. Previous treatment: Previously on drugs, not responsive (A Clinical Global Impression Severity Rating (CGI) of 3 (moderate severity) or greater at baseline, and on a stable dose (defined as no change in dose for at least 2 months) of an FDA-approved medication).
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Mixed medication - Non-specific medication. Stable dose (defined as no change in dose for at least 2 months) of an FDA-approved medication + (watchful waiting) Duration 4 months. Concurrent medication/care: - Comments: patients already on medication before start trial (n=46) Intervention 2: Pharma + non-pharma - Mixed medication + CBT. medication: stable dose (defined as no change in dose for at least 2 months) of an FDA-approved medication CBT: CBT: seven modules of treatment over 12 sessions, 10 of which were 1:1 with the therapist and adolescent, and two of which also included the parent. Modules included (1) Psychoeducation and Organization/ Planning (four sessions): orienting adolescents to the CBT model, psychoeducation about ADHD, and organizing and planning skills. (2) Distractibility (two sessions). (3) Adaptive Thinking (two sessions). (4) Procrastination (one session). (5) Parent–Adolescent Sessions (two sessions) These sessions consisted of psychoeducation about ADHD for the parents, with the goal of the parents being able to help to extend the treatment outside of the sessions (6) Parent-only sessions (two optional sessions) (7) Relapse prevention (1 session). Duration 4 months. Concurrent medication/care: -
Funding	Academic or government funding (supported by NIMH grant and additional support data analysis by NIH grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CBT + MEDICATION versus MEDICATION ALONE

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome: ADHD symptoms total, parent rating (ADHD rating scale) at 4 months; Mean; -10.93 (95%CI -12.93 to -8.93) ADHD rating scale 0-54 Top=High is poor outcome, Comments: mean = estimated effect of CBT on outcome measures (longitudinal general linear mixed effects model);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - cross-over: no washout period and possible carry over effect of CBT in group adolescents who started

Study	Sprich 2016[55]
with CBT and thereafter received watchful waiting. However, results seems to show a greater effect of CBT in group adolescents who started with watchful waiting; Indirectness of outcome: No indirectness ; Baseline details: cross over trial: all patients received both treatment arms; Group 1 Number missing: , Reason: lost to follow up/ time constraints / no longer living in nearby area; Group 2 Number missing: - Actual outcome: ADHD symptoms total, adolescent rating (ADHD rating scale) at 4 months; Mean; -5.24 (95%CI -7.21 to -3.28) ADHD rating scale 0-54 Top=, Comments: mean = estimated effect of CBT on outcomes (longitudinal general linear mixed effects model); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - cross-over: no washout period and possible carry over effect of CBT in group adolescents who started with CBT and thereafter received watchful waiting. However, results seems to show a greater effect of CBT in group adolescents who started with watchful waiting; Indirectness of outcome: No indirectness ; Baseline details: cross over trial: all patients received both treatment arms; Group 1 Number missing: , Reason: lost to follow up/ time constraints / no longer living in nearby area; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study (subsidiary papers)	Storebo 2012[56] (Storebo 2011[57])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in Denmark; Setting: outpatient
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months (FU)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ADHD according to DSM-IV; children screened at entry by the Schedule for Affective Disorders and Schizophrenia for School-aged Children (KSADS).
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define

Study (subsidiary papers)	Storebo 2012[56] (Storebo 2011[57])
Recruitment/selection of patients	children suspected to have an attention deficit hyperactivity disorder and were referred to the Child Psychiatric Clinics were screened according to the inclusion criteria
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: unknown
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (-). 2. Age: Children 6-12 (8-12). 3. Previous treatment: Naive (children had never previously received medical treatment for ADHD).
Indirectness of population	--
Interventions	(n=28) Intervention 1: Pharma + non-pharma - Mixed medication + coaching/mentoring/psychoeducation/counselling. The experimental intervention. The children were taught how to adjust their verbal and nonverbal behaviour in their social interaction. Social-skills training also included efforts to change the child's cognitive assessment of the 'social world'. The training generally focused on teaching the children to 'read' the subtle cues in social interaction, such as learning to wait for their turn. The children in SOSTRA were offered weekly 90 minute social-skills training sessions in a total of eight weeks. Each group included two therapists trained in social-skills training. Each session had a theme, such as self-worth, nonverbal communication, feelings, impulse control, aggression management, conflict resolution, and problem solving. Simultaneously, the parents attended parental training. The themes from the children's groups were discussed during the parental groups. The children's homework was also discussed. Standard treatment encompassed the normal practice regarding ADHD patients after diagnosis, the family was offered medical treatment for the child following a medication protocol. The treatment started with the first choice: methylphenidate; the second choice: dexamfetamine; and atomoxetine was considered in patients where there was a suspicion of abuse of dexamfetamine or a significant anxiety component change. Duration 8 weeks (social skill training); 6 months standard medical treatment. Concurrent medication/care: an educational parent group, where the parents met three times during the eight week trial and received general information about ADHD. (n=28) Intervention 2: Mixed medication - Non-specific medication. Standard treatment encompassed the normal practice regarding ADHD patients after diagnosis, the family was offered medical treatment for the child following a medication protocol. The treatment started with the first choice: methylphenidate; the second choice: dexamfetamine; and atomoxetine was considered in patients where there was a suspicion of abuse of dexamfetamine or a significant anxiety component change. Duration 6 months. Concurrent medication/care: an educational parent group, where the parents met three times during the eight week trial and received general information about ADHD.
Funding	Academic or government funding (Region's Zealand University Hospital (RESUS), Region Zealand Research Foundation, and Psychiatric Research Unit, Region Zealand. Funding was also received from the

Study (subsidiary papers)	Storebo 2012[56] (Storebo 2011[57])
	Fru C. Hermansens Foundation, Slagtermester Max Wørzner and Inger Wøzners Foundation, and TrygFonden.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SOCIAL SKILL TREATMENT + STANDARD (MEDICAL) TREATMENT versus STANDARD (MEDICAL) TREATMENT

Protocol outcome 1: ADHD symptoms - Hyperactivity at <3 months
- Actual outcome for Children and young people 5 to 18: hyperactivity score (Conners 3)
at 3 months; Group 1: mean 16.15 (SD 11.45); n=27, Group 2: mean 13.93 (SD 13.24); n=27; Conners' 3rd Edition subscale 'hyperactivity-impulsivity' (teacher rated) unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 1, Reason: no results for this measure; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 2: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: hyperactivity score (Conners 3)
at 6 months; Group 1: mean 15.21 (SD 9.58); n=28, Group 2: mean 13.37 (SD 11.86); n=27; Conners' 3rd Edition subscale 'hyperactivity-impulsivity' (teacher rated) unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: lost to follow up

Protocol outcome 3: Behaviour/function at <3 months
- Actual outcome for Children and young people 5 to 18: aggressive behavior (CBRS)
at 3 months; Group 1: mean 10 (SD 12.58); n=27, Group 2: mean 11.58 (SD 11.89); n=26; Conner's Comprehensive Behaviour Rating Scale (CBRS) subscale aggressive behavior, teacher rated unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 1, Reason: no data for this measurement; Group 2 Number missing: 2, Reason: 1x lost to follow up, 1x no data for this measurement.

Protocol outcome 4: Behaviour/function at >3 months
- Actual outcome for Children and young people 5 to 18: aggressive behavior (CBRS)
at 6 months; Group 1: mean 10.5 (SD 12.41); n=28, Group 2: mean 12.78 (SD 12.25); n=27; Conner's Comprehensive Behaviour Rating Scale (CBRS) subscale aggressive behavior, teacher rated unknown Top=High is poor outcome

Study (subsidiary papers)	Storebo 2012[56] (Storebo 2011[57])

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1x lost to follow up

Protocol outcome 5: Emotional dysregulation at <3 months
- Actual outcome for Children and young people 5 to 18: emotional distress (CBRS)
at 3 months; Group 1: mean 17.26 (SD 11.25); n=27, Group 2: mean 13.04 (SD 12.31); n=26; Conner's Comprehensive Behaviour Rating Scale (CBRS) subscale emotional distress, teacher rated unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 1, Reason: no data for this measurement; Group 2 Number missing: 2, Reason: 1x lost to follow up, 1x no data for this measurement

Protocol outcome 6: Emotional dysregulation at >3 months
- Actual outcome for Children and young people 5 to 18: emotional distress (CBRS)
at 6 months; Group 1: mean 16.79 (SD 12.09); n=28, Group 2: mean 14.44 (SD 12.51); n=27; Conner's Comprehensive Behaviour Rating Scale (CBRS) subscale emotional distress, teacher rated unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: 1x lost to follow up

Protocol outcome 7: Academic outcomes at <3 months
- Actual outcome for Children and young people 5 to 18: academic score (CBRS)
at 3 months; Group 1: mean 20.13 (SD 15.15); n=24, Group 2: mean 17.88 (SD 10.11); n=26; Conner's Comprehensive Behaviour Rating Scale (CBRS) subscale academic score, teacher rated unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 4, Reason: 4x no data for this measurement; Group 2 Number missing: 2, Reason: 1x lost to follow up, 1x no data for this measurement.

Protocol outcome 8: Academic outcomes at >3 months
- Actual outcome for Children and young people 5 to 18: academic score (CBRS)
at 6 months; Group 1: mean 21.04 (SD 11.98); n=26, Group 2: mean 21.52 (SD 12.56); n=27; Conner's Comprehensive Behaviour Rating Scale (CBRS) subscale academic scores, teacher rated unknown Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High,

Study (subsidiary papers)	Storebo 2012[56] (Storebo 2011[57])
Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: males No(%) combi treatment: 19 (67.8); standard treatment 20 (74.1) Age/year mean(SD) combi treatment 10.6(1.29); standard treatment 10.2(1.34); Group 1 Number missing: 2, Reason: 2x no data for this measurement; Group 2 Number missing: 1, Reason: 1x lost to follow up	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months

Study (subsidiary papers)	Svanborg 2009[59] (Svanborg 2009[58])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Sweden
Line of therapy	1st line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had to be stimulant-naive and not clinically assessed as being in need of immediate symptom relief.
Exclusion criteria	General impairment of intelligence, serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the previous 3 months, and ongoing use of psychoactive medication other than the study drug. Patients who required immediate pharmacotherapy or structured psychotherapy were also excluded.
Recruitment/selection of patients	Were recruited consecutively from the clinics' waiting lists.
Age, gender and ethnicity	Age - Range: 6 to 15 years. Gender (M:F): 80 male: 19 female. Ethnicity: Not stated.
Further population details	1. ADHD symptom severity: Mixed population (77.8% combined, 4% hyperactive, 18.2% inattentive). 2. Age: 3. Previous treatment: Naive (Patients had to be stimulant-naive).
Extra comments	.
Indirectness of population	No indirectness

Study (subsidiary papers)	Svanborg 2009[59] (Svanborg 2009[58])
Interventions	(n=49) Intervention 1: Pharma + non-pharma - Atomoxetine + coaching/mentoring/psychoeducation/counselling. 2 capsules every morning. In week 1 patients weighing 70kg or less received a dose of 0.5mg/kg per day, and patients weighing more than 70kg received 40mg/day. This was titrated to 1.2mg/kg after 1 week, or 80mg/day respectively. Dispensed at 6 visits, visits 2 - 7 during the active treatment phase. Duration 10 weeks. Concurrent medication/care: 4 sessions of psychoeducational training of parents in both treatment groups, aimed at improving caregivers' understanding of ADHD. Attendance was not monitored so numbers receiving this training is unknown. Consisted of four 3 hr parental group sessions and was led by 1 or 2 group leaders at each site. Indirectness: No indirectness (n=50) Intervention 2: Coaching, mentoring, psychoeducation, counselling - Psychoeducation. Dispensed at 6 visits, visits 2 - 7 during the active treatment phase. Duration 10 weeks. Concurrent medication/care: 4 sessions of psychoeducational training of parents in both treatment groups, aimed at improving caregivers' understanding of ADHD. Attendance was not monitored so numbers receiving this training is unknown. Consisted of four 3 hr parental group sessions and was led by 1 or 2 group leaders at each site. Indirectness: No indirectness
Funding	Study funded by industry (This research was funded by Eli Lilly Sweden AB.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE + PSYCHOEDUCATION versus PSYCHOEDUCATION + PLACEBO

Protocol outcome 1: Quality of life at <3 months
- Actual outcome for Children and young people 5 to 18: CHIP-CE total change scores at 10 weeks PT; Group 1: mean 6.6 (SD 8.4); n=49, Group 2: mean 5.2 (SD 8.49); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms total score ADHD-RS scale at 10 weeks PT; Group 1: mean -19 (SD 10.5); n=49, Group 2: mean -6.3 (SD 10.6); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: ADHD symptoms - Inattention at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD symptoms inattention score ADHD-RS scale at 10 weeks PT; Group 1: mean -10.3 (SD

Study (subsidiary papers)	Svanborg 2009[59] (Svanborg 2009[58])
5.6); n=49, Group 2: mean -3.8 (SD 4.5); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD symptoms hyperactivity score ADHD-RS scale at 10 weeks PT; Group 1: mean -8.7 (SD 5.6); n=49, Group 2: mean -2.5 (SD 5.66); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Academic outcomes at <3 months - Actual outcome for Children and young people 5 to 18: CHIP-CE academic performance change scores at 10 weeks PT; Group 1: mean 6.7 (SD 8.4); n=49, Group 2: mean 2.4 (SD 9.19); n=50 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=579)
Countries and setting	Conducted in USA; Setting: Summer camp, school and clinic & community care
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 months and 3 year FU
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Mental health settings, paediatricians, advertisements, and school notices.
Age, gender and ethnicity	Age - Mean (SD): 8.5 (0.8). Gender (M:F): 465 male : 114 female. Ethnicity: 351 White, 115 African American, 48 Hispanic and remainder unknown
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (Between 7 and 9.9 years old). 3. Previous treatment: Previously on drugs, mixed (178 receiving ADHD medication prior to study).
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=145) Intervention 1: Pharma + non-pharma - Mixed medication + carer/family +/- teacher training. Treatment for medication management and behavioral treatment provided. Manualised guidelines determined if and when an adjustment in one treatment should be made, versus interviewing first with the other. By treatment end combined subjects received lower total daily doses of medication than medication subjects. Duration 14 months . Concurrent medication/care: None stated. (n=144) Intervention 2: Carer and family training problem - With involvement of person with ADHD. Behavioral Treatment aimed at the child, parents and school/teachers. Behavioral treatment included parent training , child- focused treatment , and a school-based intervention organized and integrated with the school year. The parent training, based on work by Barkley and Forehand MacMahon, involved 27 group (6 families per group) and 8 individual sessions per family. It began weekly on randomization , concurrent with biweekly teacher consultation ; both were tapered over time. The same therapist- consultant conducted parent training and teacher consultation, with each therapist-consultant having a case- load of 12 families. The child-focused treatment was a summer treatment program (STP) developed by Pelham3 as a therapeutic summer camp. The 8-week, 5-days-per-week , 9-hours- per-day STP employed intensive behavioral interventions administered by counsellors/aides , supervised by the same teacher-consultants who performed parent training and teacher consultation. Behavioral interventions were delivered i n group-based recreational settings, and included a point system tied to specific rewards, time out, social reinforcement , modelling, group problem-solving , sports skills, and social skills training. Summer treatment program class- rooms provided individualized academic skills practice and reinforcement of appropriate classroom behavior.

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])
	The school-based treatment had 2 components: 10 to 16 sessions of biweekly teacher consultation focused on class- room behavior managementstrategies8 and 12weeks (60 school days) of a pan-time , behaviourally trained, para professional aide working directly with the child (methods adapted from Swanson11). The aides had been STP counsellors, and the program continued in the fall classroom, which helped LO generalize STP gains LO classrooms. Throughout the school year, a daily report card linked home and school. The daily report cardHJ9 wasa1-page teacher-completed checklist of the child's successes on specific preselected behaviors, and was brought home daily by the child to be reinforced by the parent with home-based rewards (e.g., television time, snacks). Duration 14 months. Concurrent medication/care: None stated. (n=144) Intervention 3: Mixed medication - Non-specific medication. Started with a 28 day double blind, daily switch titration of methylphenidate hydrochloride, using 5 randomly ordered repeats each of placebo, 5mg, 10 mg, 15 or 20 mg (higher doses for children >25kg). Each dose was given at breakfast and lunch with a half dose in the afternoon. Blinded clinicians reviewed graphs of parent/teacher ratings of responses to each dose to select child's best dose. After agreement blind was broken and agree dose became subjects initial dose. For subjects not obtaining an adequate response to methylphenidate during titration alternate medications were titrated openly in following order until a satisfactory one was found; dextroamphetamine, pemoline, imipramine and others approved by cross site panel if necessary. Duration 14 months. Concurrent medication/care: During half-hour monthly medication maintenance visits, pharmacotherapists provided support, encouragement and practical advice but not behavioral treatment. (n=146) Intervention 4: Coaching, mentoring, psychoeducation, counselling - Counselling. Community care participants received none of four MTA treatments, but were provided a report of their initial study assessments, along with a list of community mental health resources. Most community care subjects (n = 97, 67.4%) received ADHD medications (principally one of the stimulants) from their own provider during the 14 months: methylphenidate (n = 84), pemoline (n = 7), amphetamine (n = 6), tricyclics (n = 6) clonidine/guanfacine (n = 4), and/or buproprion (n = 1) (10 subjects received more than 1 medication) . In addition, 16 of these 97 children were treated by their physician with another antidepressant (not counting tricyclics or bupropion). For those treated with methylphenidate, the mean total l daily close at study completion was 22.6 mg, averaging 2.3 doses per day (versus 3.0 doses per day for MTA-treated subjects). Information concerning community care psychotherapeutic treatments has not yet been coded and will not be presented in this article. Duration 14 months. Concurrent medication/care: None stated.
Funding	Academic or government funding (Grants from the National Institute of Mental Health, Bethesda, M d .)

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus BEHAVIOURAL TREATMENT

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms at 36 months FU; Group 1: mean 1.2 (SD 0.53); n=127, Group 2: mean 1.27 (SD 0.57); n=127
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Teacher rated at 14 months PT; Group 1: mean 1.12 (SD 0.75); n=134, Group 2: mean 1.47 (SD 0.81); n=119
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Parent rated at 14 months PT; Group 1: mean 1.02 (SD 0.66); n=133, Group 2: mean 1.4 (SD 0.68); n=129
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Teacher rated at 14 months PT; Group 1: mean 0.75 (SD 0.71); n=134, Group 2: mean 1.1 (SD 0.77); n=119
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Parent rated at 14 months PT; Group 1: mean 1.85 (SD 0.63); n=133, Group 2: mean 1.24 (SD 0.72); n=129
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Classroom observer rated at 14 months PT; Group 1: mean 0.21 (SD 0.2); n=114, Group 2: mean 0.29 (SD 0.26); n=107
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 4: Behaviour/function at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Teacher rated at 14 months PT; Group 1: mean 0.61 (SD 0.68); n=134, Group 2: mean 0.97 (SD 0.8); n=119
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Parent rated at 14 months PT; Group 1: mean 0.76 (SD 0.64); n=133, Group 2: mean 1.05 (SD 0.74); n=129
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Classroom observer rated at 14 months PT; Group 1: mean 0.007 (SD 0.015); n=114, Group 2: mean 0.01 (SD 0.018); n=107
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD at 36 months FU; Group 1: mean 0.91 (SD 0.66); n=127, Group 2: mean 0.93 (SD 0.67); n=127
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 5: Academic outcomes at >3 months
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 14 months PT; Group 1: mean 99.4 (SD 15.2); n=136, Group 2: mean 96.2 (SD 14.9); n=134
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Mathss at 14 months PT; Group 1: mean 100.5 (SD 16.4); n=136, Group 2: mean 100.3 (SD 13.7); n=134
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 36 months FU; Group 1: mean 97.7 (SD 13.7); n=127, Group 2: mean 98.3 (SD 14.1); n=127
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus MEDICATION MANAGEMENT

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms at 36 months FU; Group 1: mean 1.2 (SD 0.53); n=127, Group 2: mean 1.21 (SD 0.58); n=115
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Teacher rated at 14 months PT; Group 1: mean 1.12 (SD 0.75); n=134, Group 2: mean 1.11 (SD 0.77); n=120
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Parent rated at 14 months PT; Group 1: mean 1.02 (SD 0.66); n=133, Group 2: mean 1.12 (SD 0.7); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Teacher rated at 14 months PT; Group 1: mean 0.75 (SD 0.71); n=134, Group 2: mean 0.82 (SD 0.69); n=120
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Parent rated at 14 months PT; Group 1: mean 1.85 (SD 0.63); n=133, Group 2: mean 0.91 (SD 0.65); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Classroom observer rated at 14 months PT; Group 1: mean 0.21 (SD 0.2); n=114, Group 2: mean 0.16 (SD 0.15); n=110
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 4: Behaviour/function at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Teacher rated at 14 months PT; Group 1: mean 0.61 (SD 0.68); n=134, Group 2: mean 0.65 (SD 0.68); n=120
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Parent rated at 14 months PT; Group 1: mean 0.76 (SD 0.64); n=133, Group 2: mean 0.94 (SD 0.74); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Classroom observer rated at 14 months

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

PT; Group 1: mean 0.007 (SD 0.015); n=114, Group 2: mean 0.004 (SD 0.011); n=108
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD at 36 months FU; Group 1: mean 0.91 (SD 0.66); n=127, Group 2: mean 0.93 (SD 0.63); n=115
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 5: Academic outcomes at >3 months
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 14 months PT; Group 1: mean 99.4 (SD 15.2); n=136, Group 2: mean 97.9 (SD 14.1); n=124
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Maths at 14 months PT; Group 1: mean 100.5 (SD 16.4); n=136, Group 2: mean 99.7 (SD 13); n=124
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 36 months FU; Group 1: mean 97.7 (SD 13.7); n=127, Group 2: mean 97.8 (SD 13.5); n=115
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus COMMUNITY CARE

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms at 36 months FU; Group 1: mean 1.2 (SD 0.53); n=127, Group 2: mean 1.26 (SD 0.61); n=116

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Teacher rated at 14 months PT; Group 1: mean 1.12 (SD 0.75); n=134, Group 2: mean 1.48 (SD 0.82); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Parent rated at 14 months PT; Group 1: mean 1.02 (SD 0.66); n=133, Group 2: mean 1.49 (SD 0.67); n=130
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Teacher rated at 14 months PT; Group 1: mean 0.75 (SD 0.71); n=134, Group 2: mean 1.25 (SD 0.84); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Parent rated at 14 months PT; Group 1: mean 1.85 (SD 0.63); n=133, Group 2: mean 1.35 (SD 0.72); n=130
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Classroom observer rated at 14 months PT; Group 1: mean 0.21 (SD 0.2); n=114, Group 2: mean 0.18 (SD 0.15); n=109
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group,

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

8 in medication group and 3 in combined group

Protocol outcome 4: Behaviour/function at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Teacher rated at 14 months PT; Group 1: mean 0.61 (SD 0.68); n=134, Group 2: mean 1 (SD 0.84); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Parent rated at 14 months PT; Group 1: mean 0.76 (SD 0.64); n=133, Group 2: mean 1.11 (SD 0.67); n=130
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Classroom observer rated at 14 months PT; Group 1: mean 0.007 (SD 0.015); n=114, Group 2: mean 0.006 (SD 0.014); n=109
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD at 36 months FU; Group 1: mean 0.91 (SD 0.66); n=127, Group 2: mean 0.97 (SD 0.71); n=116
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 5: Academic outcomes at >3 months
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 14 months PT; Group 1: mean 99.4 (SD 15.2); n=136, Group 2: mean 95.4 (SD 14.2); n=131
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Maths at 14 months PT; Group 1: mean 100.5 (SD 16.4); n=136, Group 2: mean 100.4 (SD 15.2); n=131

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 36 months FU; Group 1: mean 97.7 (SD 13.7); n=127, Group 2: mean 96 (SD 14.6); n=116

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOURAL TREATMENT versus MEDICATION MANAGEMENT

Protocol outcome 1: ADHD symptoms (total) at >3 months

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms at 36 months FU; Group 1: mean 1.27 (SD 0.57); n=127, Group 2: mean 1.21 (SD 0.58); n=115

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 2: ADHD symptoms - Inattention at >3 months

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Teacher rated at 14 months PT; Group 1: mean 1.47 (SD 0.81); n=119, Group 2: mean 1.11 (SD 0.77); n=120

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Parent rated at 14 months PT; Group 1: mean 1.4 (SD 0.68); n=129, Group 2: mean 1.12 (SD 0.7); n=121

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Teacher rated at 14 months PT; Group 1:

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

mean 1.1 (SD 0.77); n=119, Group 2: mean 0.82 (SD 0.69); n=120
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Parent rated at 14 months PT; Group 1: mean 1.24 (SD 0.72); n=129, Group 2: mean 0.91 (SD 0.65); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Classroom observer rated at 14 months PT; Group 1: mean 0.29 (SD 0.26); n=107, Group 2: mean 0.16 (SD 0.15); n=110
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 4: Behaviour/function at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Teacher rated at 14 months PT; Group 1: mean 0.97 (SD 0.8); n=119, Group 2: mean 0.65 (SD 0.68); n=120
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Parent rated at 14 months PT; Group 1: mean 1.05 (SD 0.74); n=129, Group 2: mean 0.94 (SD 0.74); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Classroom observer rated at 14 months PT; Group 1: mean 0.01 (SD 0.018); n=107, Group 2: mean 0.004 (SD 0.011); n=108
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD at 36 months FU; Group 1: mean 0.93 (SD 0.67); n=127, Group 2: mean 0.93 (SD 0.63); n=115
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 5: Academic outcomes at >3 months
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 14 months PT; Group 1: mean 96.2 (SD 14.9); n=134, Group 2: mean 97.9 (SD 14.1); n=124
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Maths at 14 months PT; Group 1: mean 100.3 (SD 13.7); n=134, Group 2: mean 99.7 (SD 13); n=124
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 36 months FU; Group 1: mean 98.3 (SD 14.1); n=127, Group 2: mean 97.8 (SD 13.5); n=115
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BEHAVIOURAL TREATMENT versus COMMUNITY CARE

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms at 36 months FU; Group 1: mean 1.27 (SD 0.57); n=127, Group 2: mean 1.26 (SD 0.61); n=116
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Teacher rated at 14 months PT; Group 1: mean 1.47 (SD 0.81); n=119, Group 2: mean 1.48 (SD 0.82); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Parent rated at 14 months PT; Group 1: mean 1.4 (SD 0.68); n=129, Group 2: mean 1.49 (SD 0.67); n=130
Risk of bias: All domain - --, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Teacher rated at 14 months PT; Group 1: mean 1.1 (SD 0.77); n=119, Group 2: mean 1.25 (SD 0.84); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Parent rated at 14 months PT; Group 1: mean 1.24 (SD 0.72); n=129, Group 2: mean 1.35 (SD 0.72); n=130
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Classroom observer rated at 14 months PT; Group 1: mean 0.29 (SD 0.26); n=107, Group 2: mean 0.18 (SD 0.15); n=109
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 4: Behaviour/function at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Teacher rated at 14 months PT; Group 1: mean 0.97 (SD 0.8); n=119, Group 2: mean 1 (SD 0.84); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group,

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])
	8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Parent rated at 14 months PT; Group 1: mean 1.05 (SD 0.74); n=129, Group 2: mean 1.11 (SD 0.67); n=130 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Classroom observer rated at 14 months PT; Group 1: mean 0.01 (SD 0.018); n=107, Group 2: mean 0.006 (SD 0.014); n=109 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD at 36 months FU; Group 1: mean 0.93 (SD 0.67); n=127, Group 2: mean 0.97 (SD 0.71); n=116 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group Protocol outcome 5: Academic outcomes at >3 months - Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 14 months PT; Group 1: mean 96.2 (SD 14.9); n=134, Group 2: mean 95.4 (SD 14.2); n=131 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Maths at 14 months PT; Group 1: mean 100.3 (SD 13.7); n=134, Group 2: mean 100.4 (SD 15.2); n=131 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 36 months FU; Group 1: mean 98.3 (SD 14.1); n=127, Group 2: mean 96 (SD 14.6); n=116 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEDICATION MANAGEMENT versus COMMUNITY CARE

Protocol outcome 1: ADHD symptoms (total) at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms at 36 months FU; Group 1: mean 1.21 (SD 0.58); n=115, Group 2: mean 1.26 (SD 0.61); n=116
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 2: ADHD symptoms - Inattention at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Teacher rated at 14 months PT; Group 1: mean 1.11 (SD 0.77); n=120, Group 2: mean 1.48 (SD 0.82); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms Inattention - Parent rated at 14 months PT; Group 1: mean 1.12 (SD 0.7); n=121, Group 2: mean 1.49 (SD 0.67); n=130
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 3, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 3: ADHD symptoms - Hyperactivity at >3 months
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Teacher rated at 14 months PT; Group 1: mean 0.82 (SD 0.69); n=120, Group 2: mean 1.25 (SD 0.84); n=128
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group
- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Parent rated at 14 months PT; Group 1: mean 0.91 (SD 0.65); n=121, Group 2: mean 1.35 (SD 0.72); n=130
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms hyperactivity - Classroom observer rated at 14 months PT; Group 1: mean 0.16 (SD 0.15); n=110, Group 2: mean 0.18 (SD 0.15); n=109

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 4: Behaviour/function at >3 months

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Teacher rated at 14 months PT; Group 1: mean 0.65 (SD 0.68); n=120, Group 2: mean 1 (SD 0.84); n=128

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Parent rated at 14 months PT; Group 1: mean 0.94 (SD 0.74); n=121, Group 2: mean 1.11 (SD 0.67); n=130

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD - Classroom observer rated at 14 months PT; Group 1: mean 0.004 (SD 0.011); n=108, Group 2: mean 0.006 (SD 0.014); n=109

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

- Actual outcome for Children and young people 5 to 18: SNAP rating scale - ADHD symptoms aggression ODD at 36 months FU; Group 1: mean 0.93 (SD 0.63); n=115, Group 2: mean 0.97 (SD 0.71); n=116

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group

Protocol outcome 5: Academic outcomes at >3 months

Study (subsidiary papers)	The MTA study trial: Anon 1999[1] (Jensen 2007[28])
- Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 14 months PT; Group 1: mean 97.9 (SD 14.1); n=124, Group 2: mean 95.4 (SD 14.2); n=131 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Maths at 14 months PT; Group 1: mean 99.7 (SD 13); n=124, Group 2: mean 100.4 (SD 15.2); n=131 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group - Actual outcome for Children and young people 5 to 18: Wechsler Individual Achievement Test - Reading at 36 months FU; Group 1: mean 97.8 (SD 13.5); n=115, Group 2: mean 96 (SD 14.6); n=116 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group; Group 2 Number missing: 6, Reason: 6 in community care group, 3 in behavioral treatment group, 8 in medication group and 3 in combined group	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Hyperactivity at <3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at <3 months

Study	Thurstone 2010[61]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in USA; Setting: outpatient
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks (PT)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria, determined with the Kiddie Schedule for Affective Disorders and Schizophrenia -

Study	Thurstone 2010[61]
	Present and Lifetime version (KSADS-PL)
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	1) age 13-19 years; 2) ability to understand and provide written, informed parental consent and minor assent, if under 18 years old, or individual consent if 18 years or older; 3) a diagnosis of ADHD using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria and an adolescent, self-report DSM-IV ADHD checklist score greater than or equal to 22; 4) DSM-IV diagnosis of at least one non-nicotine SUD, 5) plans to live locally for at least four months; and 6) willingness to participate in motivational interviewing/cognitive behavioral therapy (MI/CBT) for SUD during the medication trial.
Exclusion criteria	1) mental illness that could not be managed as an outpatient (e.g. serious suicidal ideation), or without concurrent psychotropic medication; 2) history of bipolar disorder or psychosis; 3) medical contraindication to taking atomoxetine; 4) pregnancy, breast feeding, or unwillingness to use an effective form of birth control while in the study; and 5) SUD that could not be managed as an outpatient or without concurrent psychotropic medications (e.g. alcohol withdrawal, opioid withdrawal).
Recruitment/selection of patients	unclear
Age, gender and ethnicity	Age - Mean (SD): 16.09 (1.58). Gender (M:F): 55/15. Ethnicity: Hispanic/ Latino (57%)
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Young people 12-17 (13-19 years). 3. Previous treatment: Not stated / Unclear

Study	Thurstone 2010[61]
Extra comments	adolescents with diagnosis of ADHD presenting for substance use disorder (SUD) treatment age 13-19 years a diagnosis of ADHD
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Pharma + non-pharma - Atomoxetine + CBT. Atomoxetine: started at 0.5 mg/kg to 0.75 mg/kg per day and increased by 25 mg per week until their total dose was between 1.1 mg/kg and 1.5 mg/kg. Participants weighing more than 70 kg started at 50 mg per day and increased to 75 mg per day in the second week and 100 mg in the third week. Subjects were instructed to take the study medication once daily in the morning. motivational interviewing/cognitive behavioral therapy(MI/CBT) for substance use disorder SUD: The MI/CBT consisted of hour-long, weekly individual sessions and could include up to three family sessions. Cognitive, behavioral, and motivational techniques were used to help adolescents reduce their drug use and improve coping. Core modules included goal setting, a functional analysis of drug use, and coping with cravings. Subsequent modules included anger management, communication skills, mood management, drug refusal skills, and problem solving. The principal investigator and one of the research therapists were trained by the manual's developers. The principal investigator then trained the other five research therapists. Each therapist was audiotaped at least once during the study and chose a convenient session for the taping. Duration 12 weeks (PT). Concurrent medication/care: unknown (n=35) Intervention 2: Cognitive behavioural therapies - CBT. placebo and motivational interviewing/cognitive behavioral therapy(MI/CBT) for substance use disorder SUD: The MI/CBT consisted of hour-long, weekly individual sessions and could include up to three family sessions. Cognitive, behavioral, and motivational techniques were used to help adolescents reduce their drug use and improve coping. Core modules included goal setting, a functional analysis of drug use, and coping with cravings. Subsequent modules included anger management, communication skills, mood management, drug refusal skills, and problem solving. The principal investigator and one of the research therapists were trained by the manual's developers. The principal investigator then trained the other five research therapists. Each therapist was audiotaped at least once during the study and chose a convenient session for the taping. Duration 12 weeks (PT). Concurrent medication/care: unknown
Funding	Academic or government funding (the American Academy of Child and Adolescent Psychiatry Physician Scientist Program in Substance Abuse K12 Award (and National Institute on Drug Abuse grants. Medication and matching placebo were supplied by Eli Lilly)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE + CBT versus PLACEBO + CBT	

Study	Thurstone 2010[61]
Protocol outcome 1: ADHD symptoms (total) at <3 months - Actual outcome for Children and young people 5 to 18: DSM-IV ADHD symptom checklist (adolescent) at 12 weeks (PT); Group 1: mean 18.19 - (SD 13.26); n=32, Group 2: mean 19.02 - (SD 14.24); n=33; DSM-IV ADHD symptom checklist 0-54 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 21% female, mean age 16.1 years (SD 1.6), baseline adolescent ADHD score 40.03 (SD 8.0), ; Group 1 Number missing: 3, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up - Actual outcome for Children and young people 5 to 18: DSM-IV ADHD symptom checklist (parents) at 12 weeks (PT); Group 1: mean 13.82 - (SD 12.79); n=32, Group 2: mean 8.82 - (SD 15.38); n=33; DSM-IV ADHD symptoms checklist 0-54 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 21% female, mean age 16.1 years (SD 1.6), baseline adolescent ADHD score 40.03 (SD 8.0), ; Group 1 Number missing: 3, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up Protocol outcome 2: CGI-I at <3 months - Actual outcome for Children and young people 5 to 18: CGI-I (physician) at 12 weeks (PT); Group 1: 17/32, Group 2: 20/33 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 21% female, mean age 16.1 years (SD 1.6), baseline adolescent ADHD score 40.03 (SD 8.0), ; Group 1 Number missing: 3, Reason: lost to follow up; Group 2 Number missing: 2, Reason: lost to follow up	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Van der oord 2007[62]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Netherlands; Setting: Psychiatric outpatient clinics
Line of therapy	1st line

Study	Van der oord 2007[62]
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic Interview Schedule for children (DISC-IV)
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	a DSM-IV diagnosis of ADHD and an estimated full scale IQ of 75 or above
Exclusion criteria	Inadequate mastering of the Dutch language by the child or both parents, and a history of methylphenidate use. Before participation children gave their verbal and parents their written informed consent
Recruitment/selection of patients	Psychiatric outpatient clinics
Age, gender and ethnicity	Age - Mean (SD): 9.9 (1.2). Gender (M:F): 40/5. Ethnicity: Not reported
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (ADHD (DBDRS). Med versus Med+Beh (Mean (SD)) 30.5 (9.5) versus 27.56 (7.62)). 2. Age: Children 6-12 3. Previous treatment: Naive (Participants had no history of methylphenidate us. No information on non-pharma).
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: CNS stimulants - Methylphenidate. A four-week pseudo randomized multiple blind placebo controlled crossover medication design, as described for the MTA study, was used for individual methylphenidate dose titration. In this titration trial 5, 10, and 20 mg of methylphenidate and placebo were administered in a pseudo random order twice daily at breakfast (around 7.30 a.m.) and at lunch (around 12.30 p.m.). All children weighed above 22 kg, thus the highest dose never exceeded 0.9 mg per kg of the body weight. All children started with a lead-in phase of 4 days to assess side effects, starting with placebo, followed by 5, 10, and finally 20 mg of methylphenidate, twice a day. None of the children showed significant side effects. Then, 4 weeks of medication titration started. Of the remaining 44 children, 25 (59%) were assigned to an individually optimally titrated dose of methylphenidate, with an average individual dose of 20.8 mg/day (SD = 10.18). The remaining 19 children were classified as placebo-responders. Manualized instructions for psychiatrists included the option of prescribing 5 mg twice daily for placebo-responders, in case of recurring ADHD symptoms during the medication-free week. Using this procedure, eight children were prescribed 5 mg twice a day. . Duration 10 weeks. Concurrent medication/care: No other treatment

Study	Van der oord 2007[62]
	(n=27) Intervention 2: Pharma + non-pharma - Stimulants + carer/family +/- teacher training. Pharma (see details in the Methylphenidate arm) The multimodal behavior therapy integrated family based and school-based interventions with cognitive behavior therapy of the child. The multimodal behavior therapy started in the first week of medication titration. Treatment selection was based on empirical efficacy in reducing ADHD or related symptoms and applicability in outpatient settings. Parent behavior therapy. The parent behavior therapy consisted of 10 weekly sessions of 90 min group therapy for four or five parent couples, provided by two therapists. The parent training was based on Barkley's training: ''Defiant children: A clinicians manual for parent training''. Components included psycho-education on ADHD, structuring the environment, practicing positive attending skills, giving effective behavioral commands to the child, contingency management skills, and knowledge of parenting techniques such as time-out. Teacher behavioral training. The teacher training was based on the teachers training manual by Pelham: ''Attention deficit hyperactivity disorder, diagnosis, nature, aetiology and treatment'' [35]. The teacher training consisted of a two-hour workshop, in which psycho-education on ADHD, structuring the classroom environment, implementing contingency management in the classroom, and a daily report card (DRC) system were explained to the teacher. The DRC is a classroom contingency management technique where parents provide rewards based on the teacher's ratings of the child's classroom behavior for that day. Teachers received an extensive handout of the training and weekly additional contacts by phone, during which the implementation of behavioral techniques was monitored, the use of the DRC was evaluated, and possible problems were discussed. Child cognitive-behavior therapy. The child cognitive behavior therapy consisted of 10 weekly 75-min group sessions for four or five children, provided by two therapists. Cognitive-behavioral techniques consisted of the children acquiring problem- solving techniques. Relaxation and contingency management techniques were also used. Training comprised modelling by the therapists, role-playing, and guided practice. Academic and interpersonal problems were extensively covered, to ensure generalization across the wide range of problem behaviors. In addition, a token reinforcement system was used during the group sessions. Duration 10 weeks. Concurrent medication/care: none
Funding	Funding not stated (Unclear)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CARER/FAMILY +/- TEACHER TRAINING versus METHYLPHENIDATE Protocol outcome 1: ADHD symptoms (total) at <3 months	

Study	Van der oord 2007[62]
- Actual outcome for Children and young people 5 to 18: Disruptive Behavior Disorder Rating Scale (DBDRS) - ADHD (Parent) at 10 weeks (PT); Group 1: mean 12.86 (SD 8.08); n=24, Group 2: mean 16.9 (SD 10.77); n=21; Disruptive Behavior Disorder Rating Scale (DBDRS) - ADHD (Parent) 0-54 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education mother and father, IQ, Comorbid behavioral disorders. ; Group 1 Number missing: 3, Reason: Discontinued intervention and omitted from analysis ; Group 2 Number missing: 2, Reason: Declined intervention and no post-test - Actual outcome for Children and young people 5 to 18: Disruptive Behavior Disorder Rating Scale (DBDRS) - ADHD (Teacher) at 10 weeks (PT); Group 1: mean 15.9 (SD 10.28); n=24, Group 2: mean 13.75 (SD 8.98); n=21; Disruptive Behavior Disorder Rating Scale (DBDRS) - ADHD (Teacher) 0-54 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Sex, Age, Education mother and father, IQ, Comorbid behavioral disorders. ; Group 1 Number missing: 3, Reason: Discontinued intervention and omitted from analysis ; Group 2 Number missing: 2, Reason: Declined intervention and no post-test -
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Vidal 2015[63]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=119)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	Not clear: 12 sessions
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	DSM-IV ADHD diagnosis; age between 15 and 21 years; stabilized doses of medication for ADHD for at least two months before the study; and agreement not to seek out any other psychiatric or psychological treatment during the study.
Exclusion criteria	Presence of the following: affective disorders; anxiety disorders, psychotic disorders; personality disorders; substance use disorders in the past six months, pervasive developmental disorder (PDD); an IQ lower than 85; and concurrent psychological intervention.
Recruitment/selection of patients	Participants were recruited from the 2 ADHD units in university hospitals in Barcelona.
Age, gender and ethnicity	Age - Mean (SD): 17.47 (1.88). Gender (M:F): 81 male: 38 female. Ethnicity: Not reported.
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Young people 12-17 (Aged between 15-21). 3. Previous treatment: Not stated / Unclear
Extra comments	The only comorbidities accepted were ODD and learning disorders such as dyslexia.
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Pharma + non-pharma - Mixed medication + CBT. The CBT program was based on cognitive behavioral principles and used motivational interviewing techniques. The treatment consisted of 12 sessions. Duration 12 sessions. Concurrent medication/care: Stabilized dose of medication. (n=60) Intervention 2: Pharma + non-pharma - Mixed medication + coaching/mentoring/psychoeducation/counselling. The control group was a waiting list group. Participants were visited only to monitor their adherence and continuation on medications for ADHD as prescribed by their psychiatrist. Participants did not receive any CBT or other type of psychological treatment during the study period. Duration 12 sessions. Concurrent medication/care: Stabilized dose of medication.

Study	Vidal 2015[63]
Funding	Academic or government funding (Financial support received from the Agencia de Salut Publica de Barcelona and the Department de Salut, Government of Catalonia, Spain and a grant from the Agressotype Research Program.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + CBT versus MIXED MEDICATION + USUAL CARE

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD-RS Adolescent Total Score at Post intervention, after 12 sessions; Group 1: mean 18.47 (SD 1.01); n=59, Group 2: mean 26.09 (SD 1.02); n=60; Comments: The clinician-administered version was used for the adolescent and parent informant.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: CBT group - 27.28, Control - 27.45; Group 1 Number missing: 14, Reason: 2 - Withdrew post randomization, 6 - discontinued medication, 6 - dropped out ; Group 2 Number missing: 16, Reason: 1 - withdrew post randomisation, 4 - lost at post treatment assessment, 6 - discontinued medication, 5 - dropped out
- Actual outcome for Children and young people 5 to 18: ADHD-RS Parents Total Score at Post intervention, after 12 sessions; Group 1: mean 19.05 (SD 1.11); n=59, Group 2: mean 28.44 (SD 1.13); n=60; Comments: The clinician-administered version was used for the adolescent and parent informant.
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: CBT group - 29.05, Control - 29.32; Group 1 Number missing: 14, Reason: 2 - Withdrew post randomization, 6 - discontinued medication, 6 - dropped out ; Group 2 Number missing: 16, Reason: 1 - withdrew post randomisation, 4 - lost at post treatment assessment, 6 - discontinued medication, 5 - dropped out

Protocol outcome 2: ADHD symptoms - Inattention at <3 months
- Actual outcome for Children and young people 5 to 18: ADHD-RS Adolescent Inattention at Post intervention, after 12 sessions; Group 1: mean 10.14 (SD 0.51); n=59, Group 2: mean 14.47 (SD 0.5); n=60; Comments: The clinician-administered version was used for the adolescent and parent informant.

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: CBT group - 15.47, Control - 14.83; Group 1 Number missing: 14, Reason: 2 - Withdrew post randomization, 6 - discontinued medication, 6 - dropped out ; Group 2 Number missing: 16, Reason: 1 - withdrew post randomisation, 4 - lost at post treatment assessment, 6 - discontinued medication, 5 - dropped out
- Actual outcome for Children and young people 5 to 18: ADHD-RS Parents Inattention at Post intervention, after 12 sessions; Group 1: mean 11.31 (SD 0.58); n=59, Group 2: mean 16.99 (SD 0.6); n=60; Comments: The clinician-administered version was used for the adolescent and parent informant.

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: CBT group - 17.27, Control - 17.03; Group 1 Number missing: 14, Reason: 2

Study	Vidal 2015[63]
- Withdrew post randomization, 6 - discontinued medication, 6 - dropped out ; Group 2 Number missing: 16, Reason: 1 - withdrew post randomisation, 4 - lost at post treatment assessment, 6 - discontinued medication, 5 - dropped out Protocol outcome 3: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: ADHD-RS Adolescent Impulsivity at Post intervention, after 12 sessions; Group 1: mean 8.29 (SD 0.7); n=59, Group 2: mean 11.72 (SD 0.7); n=60; Comments: The clinician-administered version was used for the adolescent and parent informant. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: CBT group - 11.83, Control - 12.36; Group 1 Number missing: 14, Reason: 2 - Withdrew post randomization, 6 - discontinued medication, 6 - dropped out ; Group 2 Number missing: 16, Reason: 1 - withdrew post randomisation, 4 - lost at post treatment assessment, 6 - discontinued medication, 5 - dropped out - Actual outcome for Children and young people 5 to 18: ADHD-RS Parents Impulsivity at Post intervention, after 12 sessions; Group 1: mean 7.72 (SD 0.77); n=59, Group 2: mean 11.56 (SD 0.78); n=60; Comments: The clinician-administered version was used for the adolescent and parent informant. Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: CBT group - 12, Control - 12.06; Group 1 Number missing: 14, Reason: 2 - Withdrew post randomization, 6 - discontinued medication, 6 - dropped out ; Group 2 Number missing: 16, Reason: 1 - withdrew post randomisation, 4 - lost at post treatment assessment, 6 - discontinued medication, 5 - dropped out	
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Waxmonsky 2010[65]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in USA; Setting: outpatient
Line of therapy	1st line
Duration of study	Intervention time: 8 weeks (PT)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ADHD based on DSM-IV criteria, based on several sources of information (parents and teachers ratings on behavior disorders rating scale)

Study	Waxmonsky 2010[65]
Stratum	Children and young people 5 to 18
Subgroup analysis within study	Not applicable
Inclusion criteria	not described
Exclusion criteria	1. current or past history of seizures, 2 other physical conditions the precluded atomoxetine, 3 documented failed trial of atomoxetine, 4 serious forms of psychopathology other than ADHD, 5 any history of major depression requiring treatment, 6 IQ less than 75, 7 no evidence of ADHD related impairment at school
Recruitment/selection of patients	subjects recruited from schools, paediatric offices and local community through radio and print advertisements
Age, gender and ethnicity	Age - Mean (SD): 8.59 (1.58). Gender (M:F): 80/11. Ethnicity: 5.4% Hispanic/ 94.6% non-Hispanic
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Children 6-12 (6-12 years). 3. Previous treatment: Previously on drugs, mixed (n=21 never been treated with stimulants).
Extra comments	n=7 had previously been treated with atomoxetine, included 1 who was a prior responder but had not taken it for > 1 year. The efficacy of the drug had not yet been established in all but 1 of these 7 cases.
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: Pharma + non-pharma - Atomoxetine + carer/family +/- teacher training. behavior treatment includes 3 parts: 1. parenting program (8 sessions, 2 hour each, of community oriented parent education program; teach parents techniques to promote their child's positive behavior and self-regulation), 2.social skills program (8 sessions for children, 2 hour, on cooperation, participation, validation, communication and children participated in social activities) , and 3.school-based daily report card (developed by clinical staff in consultation with the child's teacher following a standard format; specific behavioral goals were identified for each child. teachers evaluated child's performance on these days multiple times during the day. teachers provided child with feedback about performance. atomoxetine: started on 0.5 mg/kg/d for 3 days, the 0.8 mk/kg/d for next 4 days, on day 8 increased to 1.2 mg/kg/d. Duration 8 weeks. Concurrent medication/care: no information (n=27) Intervention 2: Atomoxetine. atomoxetine: started on 0.5 mg/kg/d for 3 days, the 0.8 mk/kg/d for next 4 days, on day 8 increased to 1.2 mg/kg/d a single morning dose. Duration 8 weeks. Concurrent medication/care: no information
Funding	Study funded by industry (funded by Eli Lilly and Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE + CARER/FAMILY +/- TEACHER TRAINING versus

Study	Waxmonsky 2010[65]
ATOMOXETINE Protocol outcome 1: ADHD symptoms - Inattention at <3 months - Actual outcome for Children and young people 5 to 18: disruptive behavior disorders rating scale - ADHD inattention (parents) at 8 weeks; Group 1: mean 1.22 - (SD 0.57); n=29, Group 2: mean 1.67 - (SD 0.67); n=27; disruptive behavior disorders rating scale - Top=High is poor outcome; Comments: range subscales not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: atomoxetine: 29.6 % stimulant native; combination: 44.8% stimulant naive ; Group 1 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."; Group 2 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses." - Actual outcome for Children and young people 5 to 18: disruptive behavior disorders rating scale - ADHD inattention (teacher) at 8 weeks; Group 1: mean 1.12 - (SD 0.77); n=29, Group 2: mean 1.35 - (SD 0.66); n=27; Comments: range not reported Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: atomoxetine: 29.6 % stimulant native; combination: 44.8% stimulant naive ; Group 1 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."; Group 2 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses." Protocol outcome 2: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Children and young people 5 to 18: disruptive behavior disorders rating scale - ADHD hyperactive (parents) at 8 weeks; Group 1: mean 0.95 - (SD 0.61); n=29, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: atomoxetine: 29.6 % stimulant native; combination: 44.8% stimulant naive ; Group 1 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."; Group 2 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses." - Actual outcome for Children and young people 5 to 18: disruptive behavior disorders rating scale - ADHD hyperactive (teacher) at 8 weeks; Group 1:	

Study	Waxmonsky 2010[65]
	mean 0.96 - (SD 0.83); n=29, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: atomoxetine: 29.6 % stimulant native; combination: 44.8% stimulant naive ; Group 1 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."; Group 2 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses." Protocol outcome 3: CGI-I at <3 months - Actual outcome for Children and young people 5 to 18: CGI at 8 weeks; Group 1: 16/29, Group 2: 14/27 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: atomoxetine: 29.6 % stimulant native; combination: 44.8% stimulant naive ; Group 1 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."; Group 2 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses." Protocol outcome 4: Behaviour/function at <3 months - Actual outcome for Children and young people 5 to 18: daily report card - behavior (teacher) at 8 weeks; Group 1: mean 82.9 total percent of goals reached each week (SD 15.13); n=29, Group 2: mean 77.84 total percent of goals reached each week (SD 21.01); n=27; - 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: atomoxetine: 29.6 % stimulant native; combination: 44.8% stimulant naive ; Group 1 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."; Group 2 Number missing: , Reason: n=7 discontinued prior to completion (5 in combination therapy, 2 in atomoxetine); 4 because patient believed medication was ineffective, 2 refused ongoing medication, 1 due to parental concerns over increased emotional lability. Unclear how much data were missing. "all available data for subjects who stopped early were included in analyses."
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at <3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months;

Study	Waxmonsky 2010[65]
	Discontinuation due to adverse effects at >3 months; Behaviour/function at >3 months; Emotional dysregulation at <3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Weiss 2012[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Canada, USA; Setting:
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 weeks and FU week 15 and 20
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Participants were recruited from the patient pool in the ADHD clinics at the Montreal Children's Hospital, Children's and Women's Health Centre in British Columbia, Yale University, Centre for Addictions and Mental Health, Toronto, and Duke University Medical Centre.
Age, gender and ethnicity	Age - Mean (SD): 35.6 (9.9). Gender (M:F): Define. Ethnicity: Not stated.
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear (Those with a primary diagnosis.). 2. Age: Adults 18-65 3. Previous treatment: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Pharma + non-pharma - Stimulants + CBT. Treatment was developed and manualised in a series of weekly telephone conference calls with the principal investigators and the clinicians involved in the study. The manual documented the approach (structures, skills based, problem focused), and methods of managing possible challenges in treatment and provided modules for addressing specific issues such as emotional dysregulation, sleep, addiction, anger outbursts and other problems common in ADHD. Therapy was administered individually for nine sessions. First session took place following the completion of titration of medication when the patient was on a stable dose. First session provided psycho education explaining ADHD as a neurobiological disorder and helping the patient understand the relationship between symptoms,

Study	Weiss 2012[66]
	his/her life story and current functional impairments. Patients were seen in acute treatment every 2 weeks (for 7 sessions) and then twice in follow up booster sessions at weeks 15 and 20. Problem Focused Therapy. The therapy manual described the psycho education session, the approach of the therapy, common problems experienced in therapy with patients with ADHD and approaches to the most common problems selected by patients. Specific modules were developed to be referenced by the therapy as appropriate for the problem the patient described. Format included review of implementation of skills from the past week, a review of symptoms, discussion of success or difficulty with implementation of the skills already covered and introduction of new skills for the week to follow. The booster sessions highlighted for the patient the specific skills that had been acquired in dealing with the problem they had chosen and ways in which the same skill set could also be applied to other areas of impairment in the patient's life. The therapy employed the key principles of CBT in challenging cognitive distortions such as personalization, over generalization, selective attention, disqualifying benefits, jumping to conclusions, should statements and catastrophizing - all of which are common in ADHD adults. Therapists were permitted to be flexible and draw on other types of psychological intervention. Medication treatment - was encapsulated so that patients could not distinguish between active and placebo. Stimulant was Dextroamphetamine dosed twice daily. Placebo also dosed twice daily. Medication was titrated by weekly increments to optimal dose over a 4 week period. Duration 14 weeks. Concurrent medication/care: All patients received individual cognitive behavioral therapy (CBT). Comments: Compliance measured by attending 8 of the 9 sessions minimum and take 80% of medication in order to remain in the protocol. Medication adherence measured by pill counts on the study bottles which were returned by the patient at each visit. (n=25) Intervention 2: Cognitive behavioural therapies - CBT. Treatment was developed and manualised in a series of weekly telephone conference calls with the principal investigators and the clinicians involved in the study. The manual documented the approach (structures, skills based, problem focused), and methods of managing possible challenges in treatment and provided modules for addressing specific issues such as emotional dysregulation, sleep, addiction, anger outbursts and other problems common in ADHD. Therapy was administered individually for nine sessions. First session took place following the completion of titration of medication when the patient was on a stable dose. First session provided psycho education explaining ADHD as a neurobiological disorder and helping the patient understand the relationship between symptoms, his/her life story and current functional impairments. Patients were seen in acute treatment every 2 weeks (for 7 sessions) and then twice in follow up booster sessions at weeks 15 and 20. Problem Focused Therapy. The therapy manual described the psycho education session, the approach of the therapy, common problems experienced in therapy with patients with ADHD and approaches to the most common problems selected by patients. Specific modules were developed to be referenced by the therapy as appropriate for the problem the patient described. Format included review of implementation of skills from the past week, a review of symptoms, discussion of success or difficulty with implementation of the skills

Study	Weiss 2012[66]
	already covered and introduction of new skills for the week to follow. The booster sessions highlighted for the patient the specific skills that had been acquired in dealing with the problem they had chosen and ways in which the same skill set could also be applied to other areas of impairment in the patient's life. The therapy employed the key principles of CBT in challenging cognitive distortions such as personalization, over generalization, selective attention, disqualifying benefits, jumping to conclusions, should statements and catastrophizing - all of which are common in ADHD adults. Therapists were permitted to be flexible and draw on other types of psychological intervention. Medication treatment - was encapsulated so that patients could not distinguish between active and placebo. Placebo dosed twice daily. Medication was titrated by weekly increments to optimal dose over a 4 week period. . Duration 14 weeks. Concurrent medication/care: All patients received individual cognitive behavioral therapy (CBT).
Funding	Study funded by industry (This project was funded by GlaxSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STIMULANTS + CBT versus CBT + PLACEBO

Protocol outcome 1: ADHD symptoms (total) at <3 months
- Actual outcome for Adults over 18: Conners Adult ADHD Rating Scales - ADHD RS-Inv at week 20 FU; Group 1: mean 20.78 (SD 9.65); n=23, Group 2: mean 23.56 (SD 12.39); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Adverse events; Group 2 Number missing: 2, Reason: Adverse events

Protocol outcome 2: CGI-I at <3 months
- Actual outcome for Adults over 18: CGI-I-ADHD at week 20 FU; Group 1: 15/23, Group 2: 4/25; Comments: Treatment responders (much or very much improved)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Adverse events; Group 2 Number missing: 2, Reason: Adverse events

Protocol outcome 3: Emotional dysregulation at <3 months
- Actual outcome for Adults over 18: HAM-D at week 20 FU; Group 1: mean 7.56 (SD 7.25); n=23, Group 2: mean 6 (SD 3.29); n=25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Adverse events; Group 2 Number missing: 2, Reason: Adverse events

Study	Weiss 2012[66]
Protocol outcomes not reported by the study	Quality of life at <3 months; Quality of life at >3 months; ADHD symptoms (total) at >3 months; ADHD symptoms - Inattention at <3 months; ADHD symptoms - Inattention at >3 months; ADHD symptoms - Hyperactivity at <3 months; ADHD symptoms - Hyperactivity at >3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Behaviour/function at <3 months; Behaviour/function at >3 months; Emotional dysregulation at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Study	Young 2015[67,68]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Iceland; Setting: Outpatient setting at Landspitali - The National University Hospital of Iceland.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM IV criteria
Stratum	Adults over 18
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 18 years old, current ADHD diagnosis, stable on prescribed ADHD medication for at least 1 month.
Exclusion criteria	Severe mental illness, severe eating disorder, active suicide ideation, active drug abuse, history of intellectual impairment.
Recruitment/selection of patients	Either hospital referrals, referrals from private practitioners, self-referrals from advertisement with national ADHD support group.
Age, gender and ethnicity	Age - Mean (SD): 35.17 (11.68). Gender (M:F): 33 male, 62 female. Ethnicity: Not specified
Further population details	1. ADHD symptom severity: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 (Age range: 18-73 years old). 3. Previous treatment: Previously on drugs, mixed
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Pharma + non-pharma - Mixed medication + CBT. R&R2ADHD. Structured manualized program consisting of 15 group sessions of 90 minutes. 2 group sessions per week. 5 treatment modules: 1) neurocognitive 2) problem solving 3) emotional control 4) prosocial skills 5) critical reasoning. Supplemented by 1 to 1 meetings with a mentor. Duration Approximately 2 months. Concurrent medication/care: Previously prescribed medication continued unchanged through study. Pharmacological

Study	Young 2015[67,68]
	usage: methylphenidate: 40, atomoxetine: 8, bupropion: 3, Other (including antidepressants, benzodiazepines, insulin, ibuprofen): 32. (n=47) Intervention 2: Pharma + non-pharma - Other. Usual care which included both pharmacological and non-pharmacological treatment. Duration Approximately 2 months. Concurrent medication/care: Previously prescribed medication continued unchanged through study. Pharmacological usage: methylphenidate: 33, atomoxetine: 8, bupropion: 2, Other (including antidepressants, benzodiazepines, insulin, ibuprofen): 31.
Funding	Other (Support for the study received from research grants from: RANNIS - the Icelandic Centre for Research, the Landspitali Science Fund, Janssen-Cilag, Iceland.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIXED MEDICATION + CBT versus MEDICATION + TREATMENT AS USUAL

Protocol outcome 1: Quality of life at <3 months
- Actual outcome for Adults over 18: QOLS 16 item scale (Flanagan) at End of treatment ; Group 1: mean 74.5 (SD 14.53); n=34, Group 2: mean 70.94 (SD 16.29); n=35
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 14, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 12, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features.

Protocol outcome 2: Quality of life at >3 months
- Actual outcome for Adults over 18: QOLS 16 item scale (Flanagan) at 3 months FU; Group 1: mean 79.84 (SD 11.07); n=25, Group 2: mean 72.22 (SD 14.31); n=32
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 22, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 15, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features.

Study	Young 2015[67,68]
Protocol outcome 3: ADHD symptoms (total) at <3 months - Actual outcome for Adults over 18: BCS combined (self-rated) at End of treatment ; Group 1: mean 17.26 (SD 7.58); n=34, Group 2: mean 21.57 (SD 9.75); n=35 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 14, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 12, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 4: ADHD symptoms (total) at >3 months - Actual outcome for Adults over 18: BCS combined (self-rated) at 3 months FU; Group 1: mean 14.72 (SD 8.31); n=25, Group 2: mean 22.34 (SD 9.17); n=32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 23, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 15, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 5: ADHD symptoms - Inattention at <3 months - Actual outcome for Adults over 18: BCS inattention (self-rated) at End of treatment; Group 1: mean 10.59 (SD 4.4); n=34, Group 2: mean 13.71 (SD 5.72); n=35 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 14, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 12, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 6: ADHD symptoms - Inattention at >3 months - Actual outcome for Adults over 18: BCS inattention (self-rated) at 3 months FU; Group 1: mean 9.6 (SD 5.34); n=25, Group 2: mean 14.19 (SD 5.85); n=32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Study	Young 2015[67,68]
Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 23, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 15, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 7: ADHD symptoms - Hyperactivity at <3 months - Actual outcome for Adults over 18: BCS hyperactivity/impulsivity (self-rated) at End of treatment ; Group 1: mean 6.68 (SD 5.01); n=34, Group 2: mean 7.86 (SD 5.92); n=35 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 14, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 12, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 8: ADHD symptoms - Hyperactivity at >3 months - Actual outcome for Adults over 18: BCS hyperactivity/impulsivity (self-rated) at 3 months FU; Group 1: mean 5.12 (SD 4.05); n=25, Group 2: mean 8.16 (SD 5.13); n=32 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 23, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 15, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 9: Behaviour/function at <3 months - Actual outcome for Adults over 18: RATE Antisocial scale at End of treatment ; Group 1: mean 9.24 (SD 1.52); n=33, Group 2: mean 10.29 (SD 2.38); n=35; RATE antisocial scale Unclear Top=High is poor outcome Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 10: Behaviour/function at >3 months - Actual outcome for Adults over 18: RATE Antisocial scale

Study	Young 2015[67,68]
at 3 months FU; Group 1: mean 8.76 (SD 1.67); n=25, Group 2: mean 11.19 (SD 4.03); n=32; RATE antisocial scale Unclear Top=High is poor outcome Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 11: Emotional dysregulation at <3 months - Actual outcome for Adults over 18: Becks Depression Inventory (BDI) - self-reported at End of treatment ; Group 1: mean 8.38 (SD 6.99); n=34, Group 2: mean 14 (SD 10.45); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 14, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 13, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. Protocol outcome 12: Emotional dysregulation at >3 months - Actual outcome for Adults over 18: Becks Depression Inventory (BDI) - self-reported at 3 months FU; Group 1: mean 5.04 (SD 5.6); n=24, Group 2: mean 13.14 (SD 7.99); n=29 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar in terms of gender, age, marital status, employment status, medical history, ADHD medication. ; Blinding details: Not possible for those receiving or giving care to be blinded due to nature of intervention. ; Group 1 Number missing: 24, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features. ; Group 2 Number missing: 18, Reason: No specific reasons given. Indicated it could be due to the nature of participants, symptom severity, practical considerations such as Icelandic weather, broader Icelandic community features.	
Protocol outcomes not reported by the study	CGI-I at <3 months; CGI-I at >3 months; Discontinuation due to adverse effects at <3 months; Discontinuation due to adverse effects at >3 months; Academic outcomes at >3 months; Academic outcomes at <3 months

Appendix E: Forest plots

E.1 Children and young people aged 5 to 18

E.1.1 Pharmacological treatment versus non-pharmacological treatment

E.1.1.1 Atomoxetine versus PT/FT

Figure 1: ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

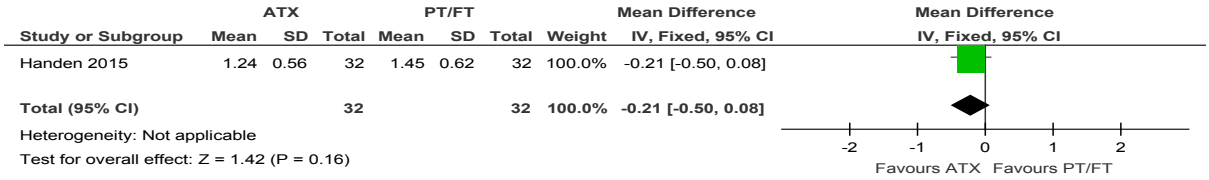


Figure 2: ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

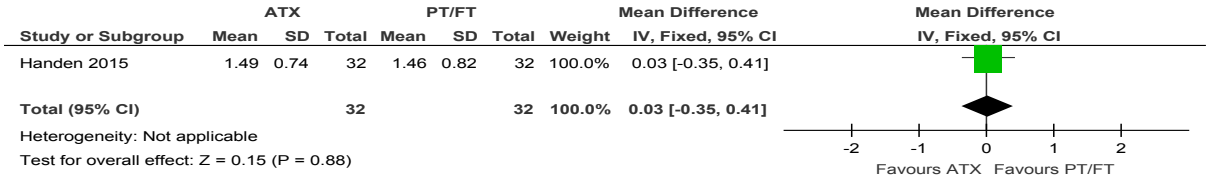


Figure 3: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

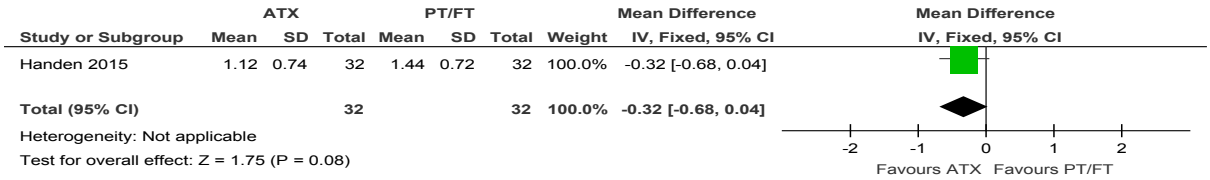


Figure 4: ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

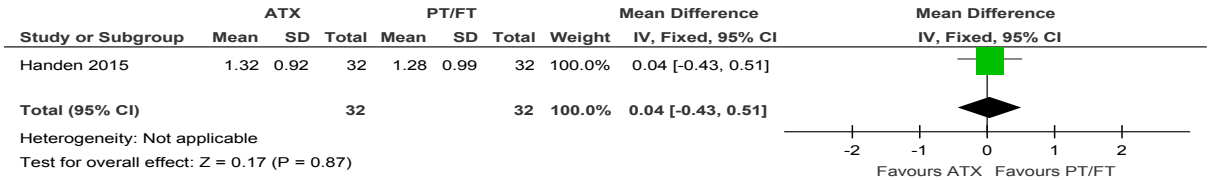


Figure 5: ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

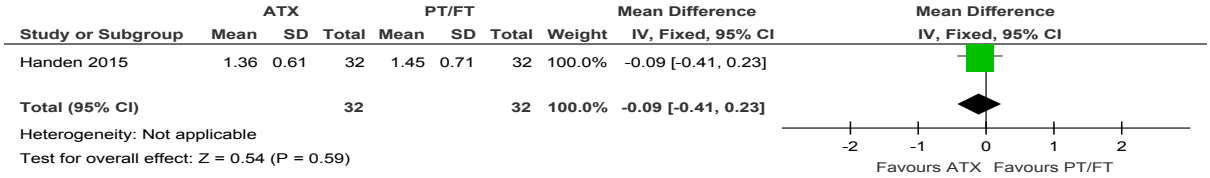


Figure 6: ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

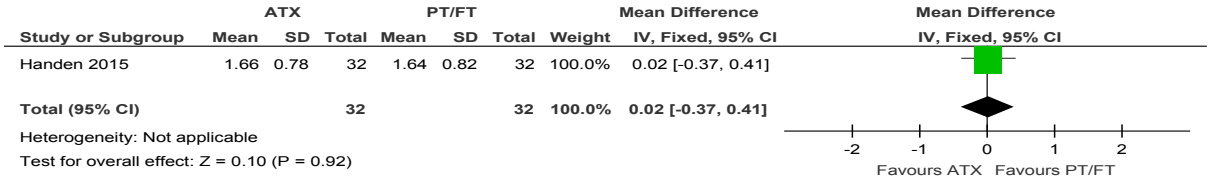
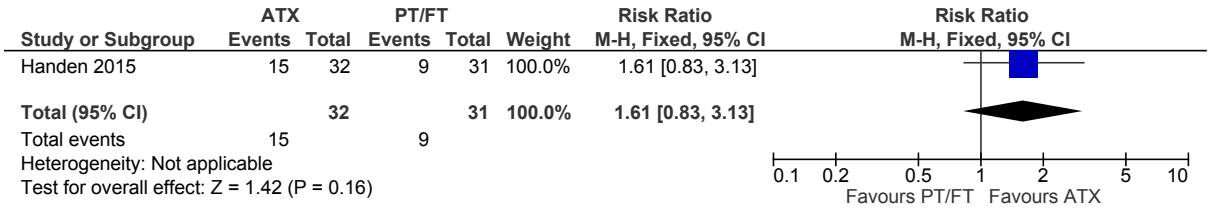


Figure 7: Responders by CGI-I (PT, <3 months)



E.1.1.2 Stimulants versus exercise

Figure 8: ADHD symptoms (hyperactivity, parent, SWAN, 0-3, high is poor, FV, PT <3 months)

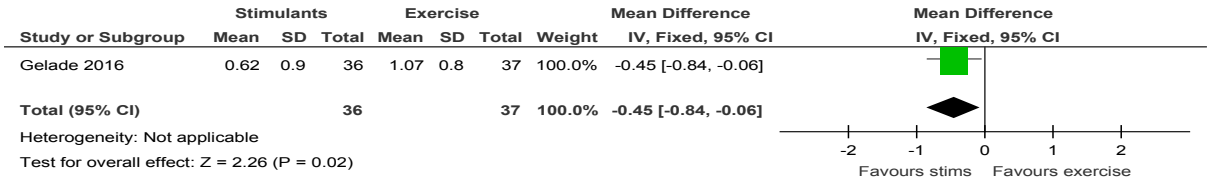


Figure 9: ADHD symptoms (hyperactivity, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)

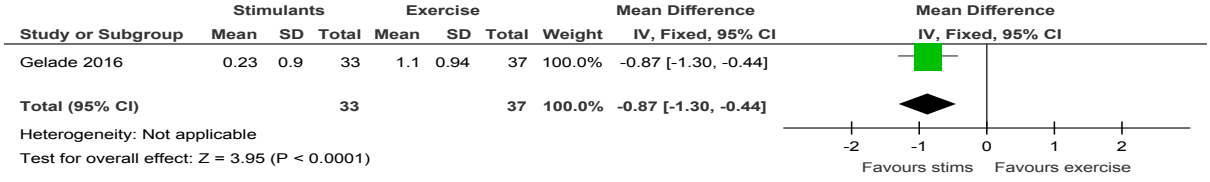


Figure 10: ADHD symptoms (inattention, parent, SWAN, 0-3, high is poor, FV, PT <3 months)

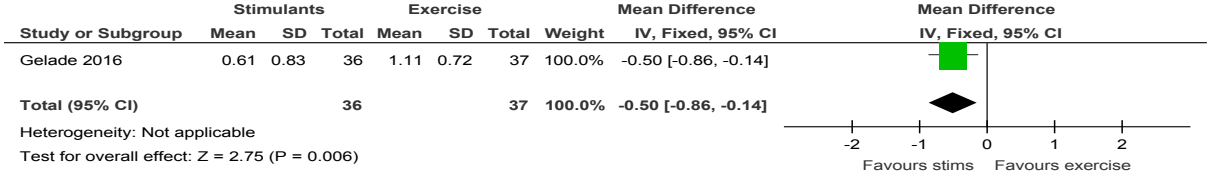
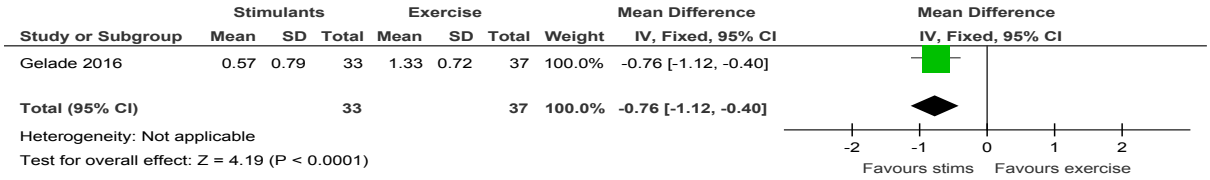


Figure 11: ADHD symptoms (inattention, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)



E.1.1.3 Stimulants versus NF

Figure 12: ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months)

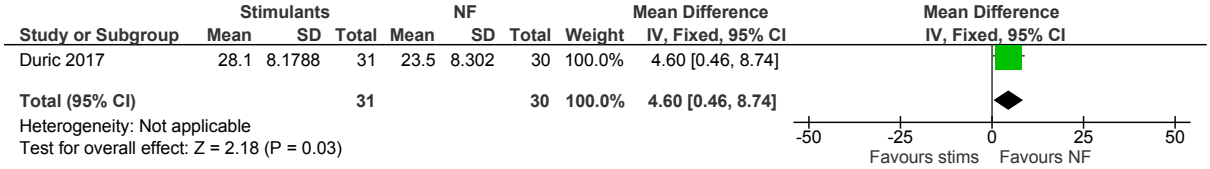


Figure 13: ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, >3 months)

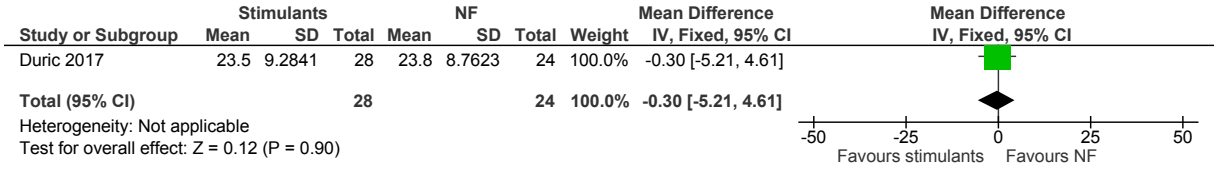


Figure 14: ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

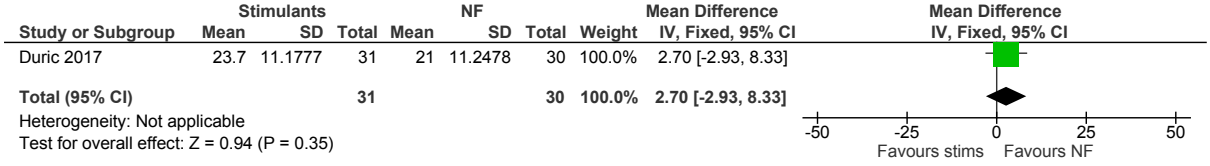


Figure 15: ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

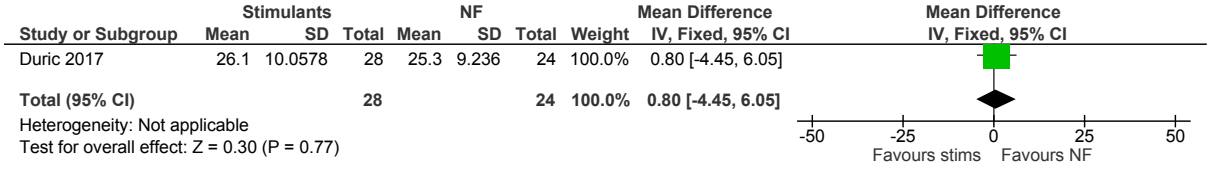


Figure 16: ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months)

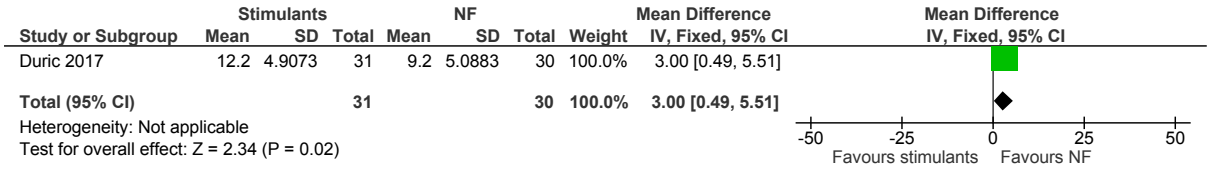


Figure 17: ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, >3 months)

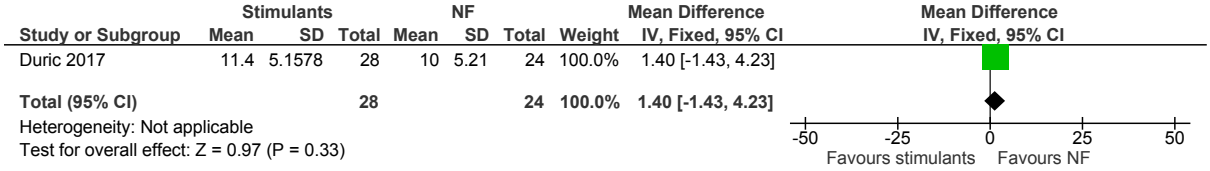


Figure 18: ADHD symptoms (hyperactivity, parent, SWAN, 0-3, high is poor, FV, PT <3 months)

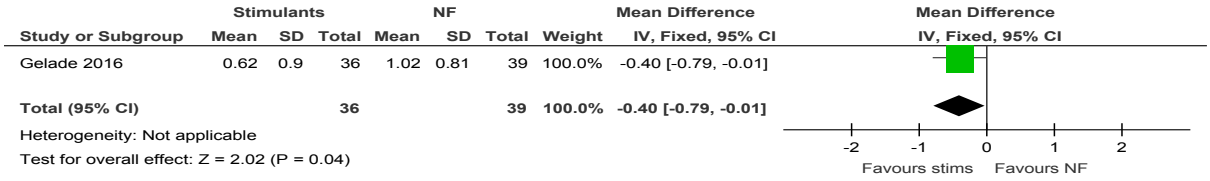


Figure 19: ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

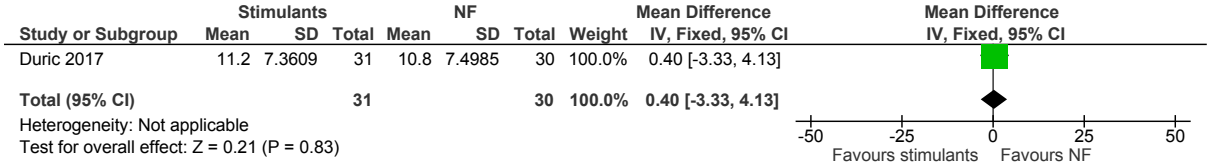


Figure 20: ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

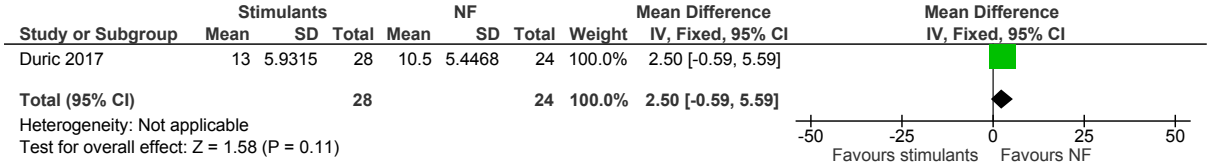


Figure 21: ADHD symptoms (hyperactivity, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)

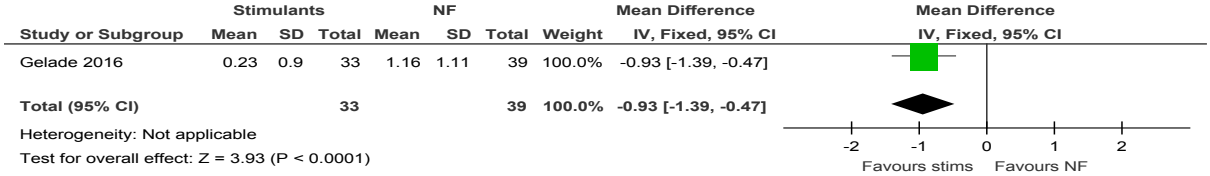


Figure 22: ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months)

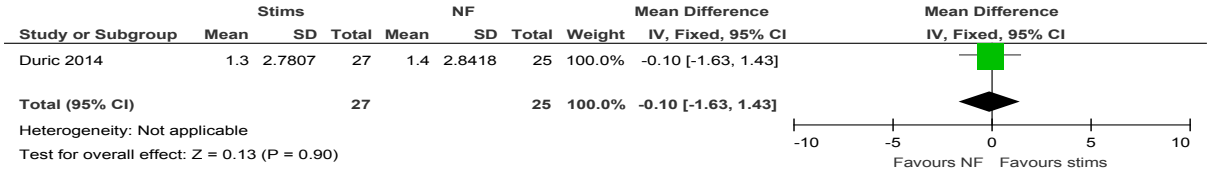


Figure 23: ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, <3 months)

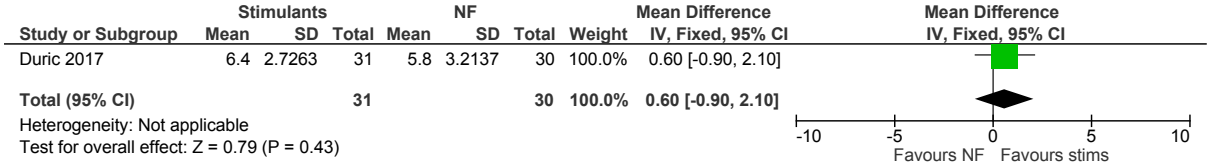


Figure 24: ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, >3 months)

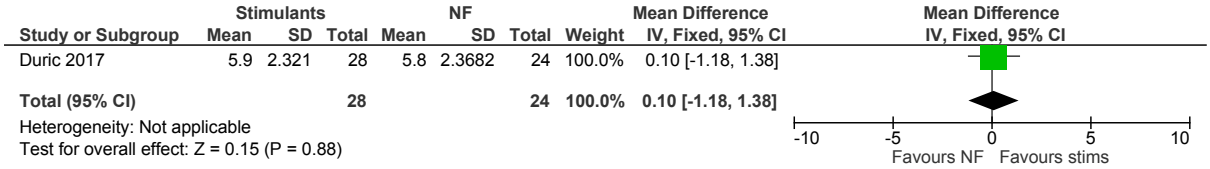


Figure 25: ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months)

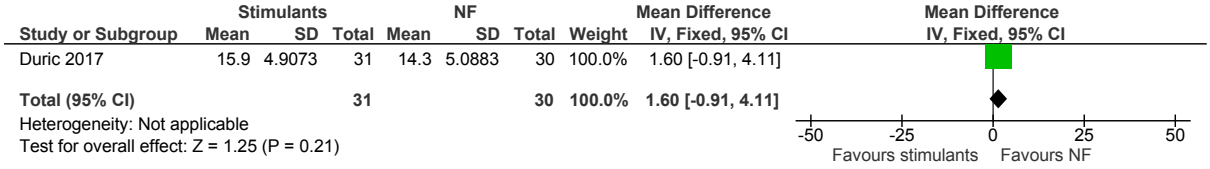


Figure 26: ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, >3 months)

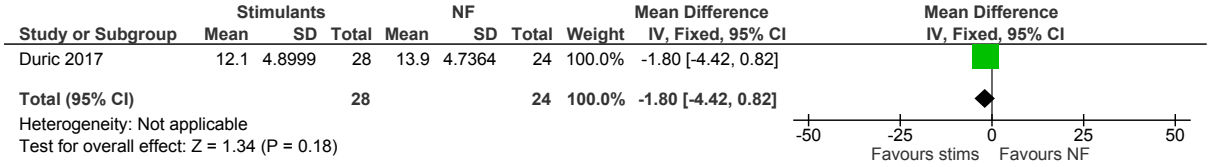


Figure 27: ADHD symptoms (inattention, parent, SWAN, 0-3, high is poor, FV, PT <3 months)

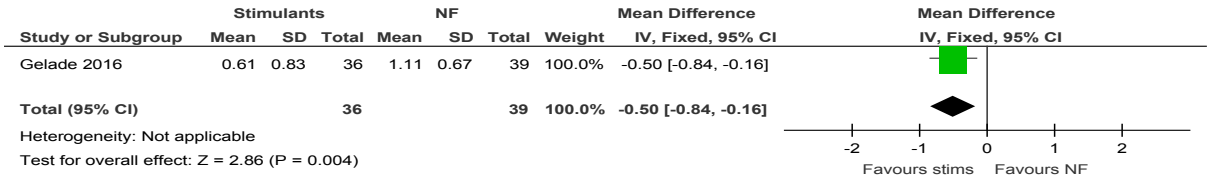


Figure 28: ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

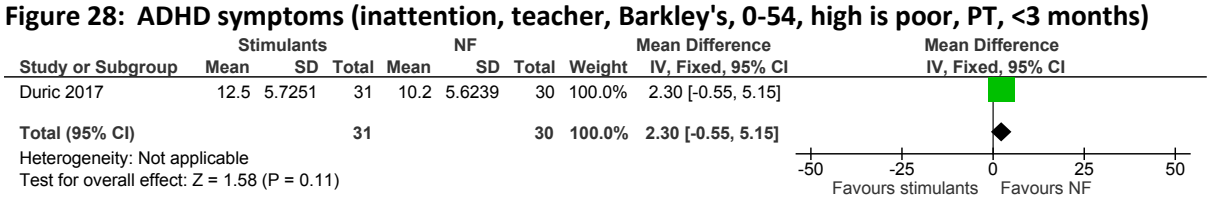


Figure 29: ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

Study or Subgroup	Stimulants Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	13.1	5.4157	28	14.8	4.9732	24	100.0%	-1.70 [-4.53, 1.13]
Total (95% CI)			**28**			**24**	**100.0%**	**-1.70 [-4.53, 1.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)

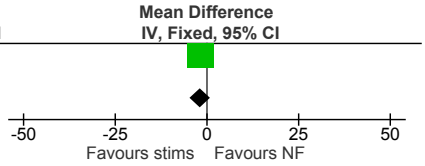


Figure 30: ADHD symptoms (inattention, teacher, SWAN, 0-3, high is poor, FV, PT <3 months)

Study or Subgroup	Stimulants Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gelade 2016	0.57	0.79	33	1.3	0.76	39	100.0%	-0.73 [-1.09, -0.37]
Total (95% CI)			**33**			**39**	**100.0%**	**-0.73 [-1.09, -0.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.98 (P < 0.0001)

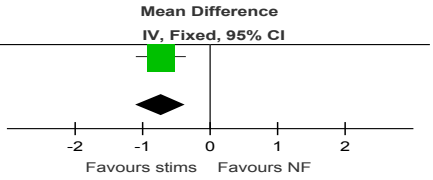


Figure 31: ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, <3 months)

Study or Subgroup	Stimulants Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	6.7	2.4536	31	6.5	2.4102	30	100.0%	0.20 [-1.02, 1.42]
Total (95% CI)			**31**			**30**	**100.0%**	**0.20 [-1.02, 1.42]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

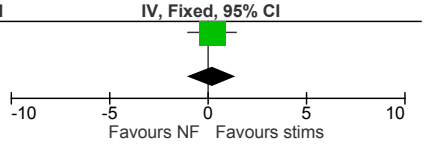


Figure 32: ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, >3 months)

Study or Subgroup	Stimulants Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	6	2.0631	28	5.6	1.8946	24	100.0%	0.40 [-0.68, 1.48]
Total (95% CI)			**28**			**24**	**100.0%**	**0.40 [-0.68, 1.48]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)

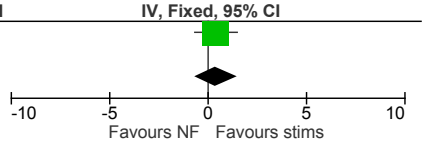


Figure 33: ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months)

Study or Subgroup	Stims Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2014	1.4	2.7807	27	1.8	2.1803	25	100.0%	-0.40 [-1.75, 0.95]
Total (95% CI)			**27**			**25**	**100.0%**	**-0.40 [-1.75, 0.95]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

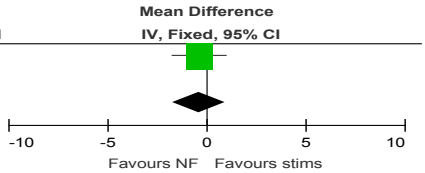


Figure 34: Academic (general, self, 1-10, high is good, CS, PT <3 months)

Study or Subgroup	Stims Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2014	0.1	3.2863	27	1.5	3.3155	24	100.0%	-1.40 [-3.22, 0.42]
Total (95% CI)			**27**			**24**	**100.0%**	**-1.40 [-3.22, 0.42]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)

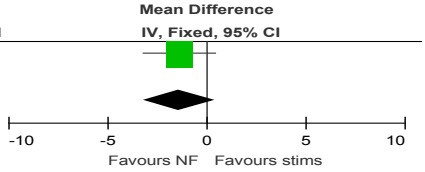


Figure 35: Academic (general, self, 1-10, high is good, PT <3 months)

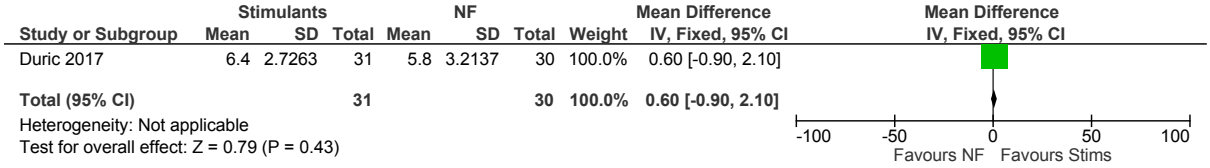
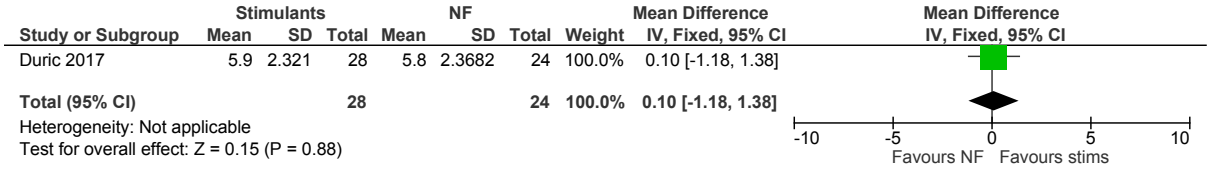


Figure 36: Academic (general, self, 1-10, high is good, PT >3 months)



E.1.1.4 Stimulants + NSST versus stimulants

Figure 37: ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, PT >3 months)

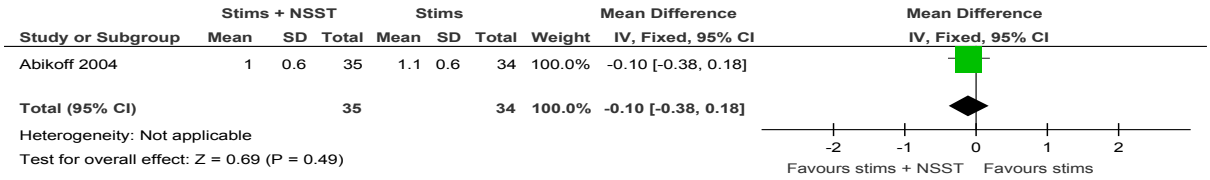


Figure 38: ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months)

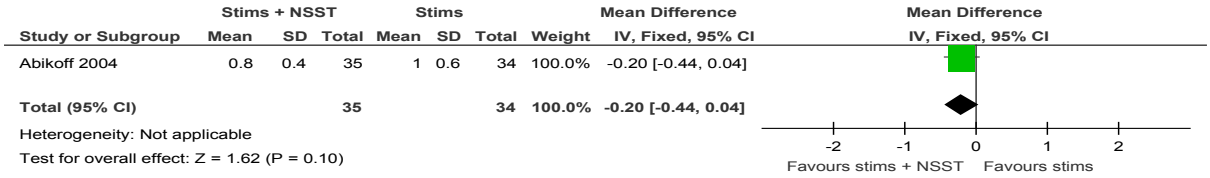


Figure 39: ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months)

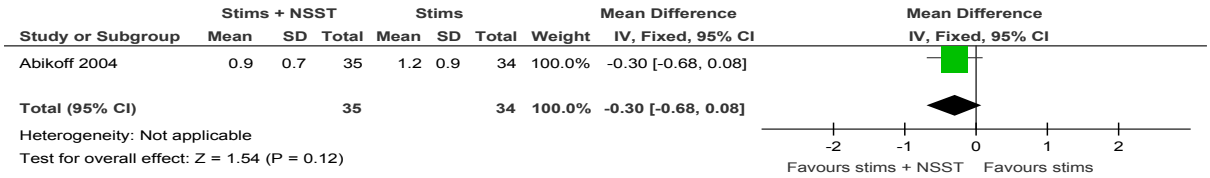
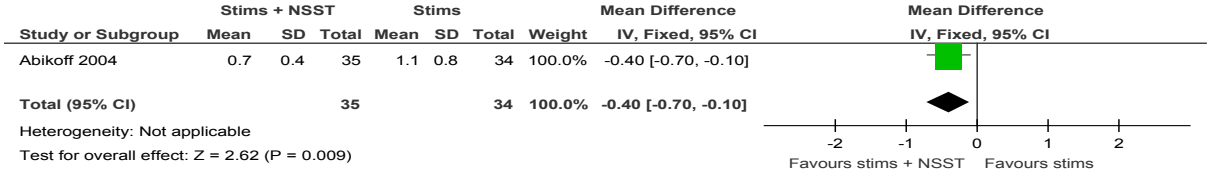


Figure 40: ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months)



E.1.1.5 Mixed medication versus PT/FT

Figure 41: ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)

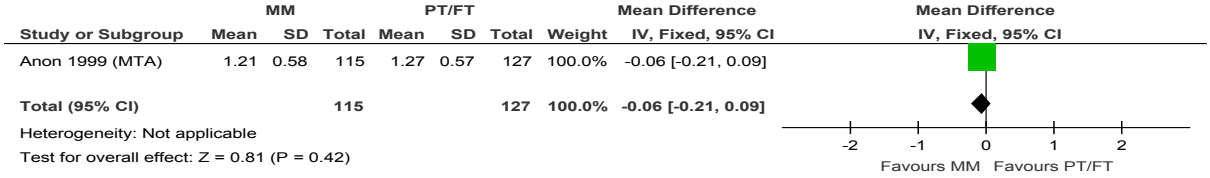


Figure 42: ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months)

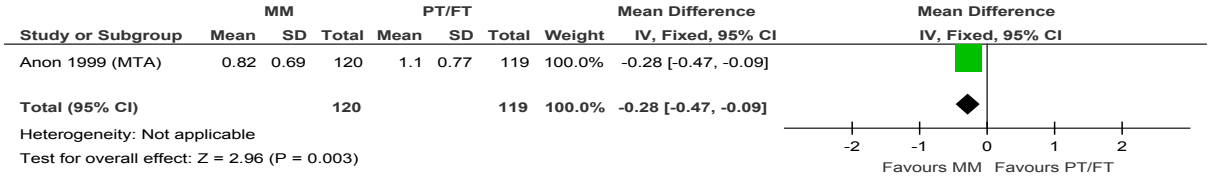


Figure 43: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

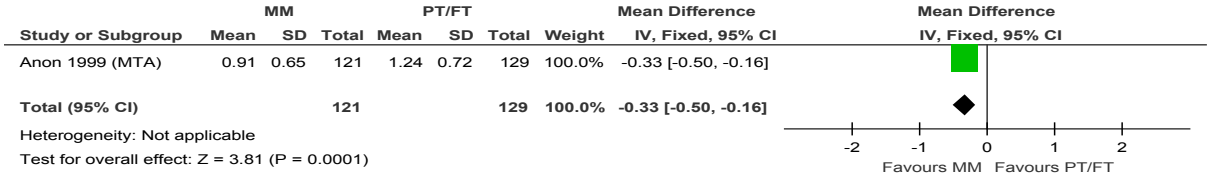


Figure 44: ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)

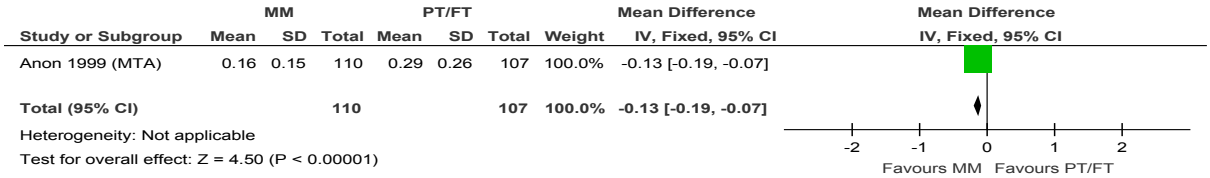


Figure 45: ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

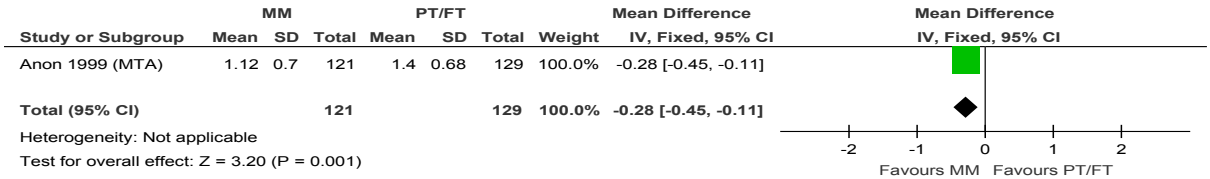


Figure 46: ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)

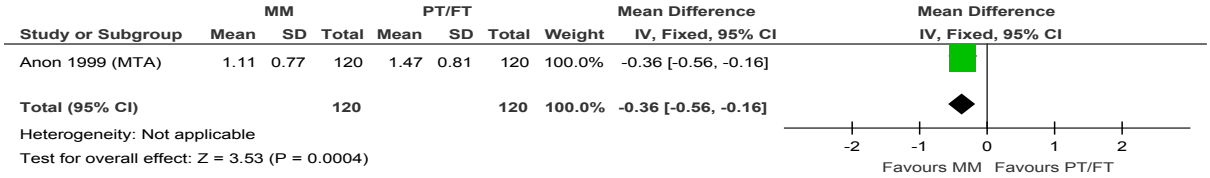


Figure 47: Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)

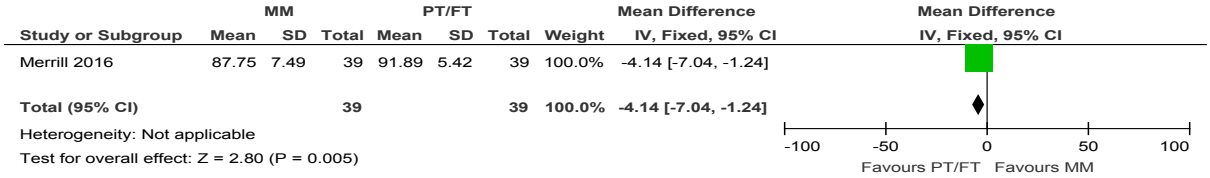


Figure 48: Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

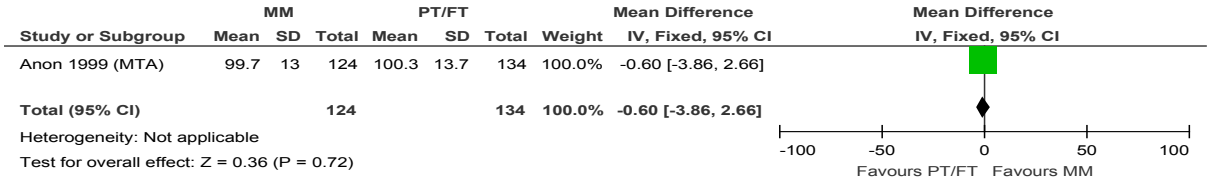


Figure 49: Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)

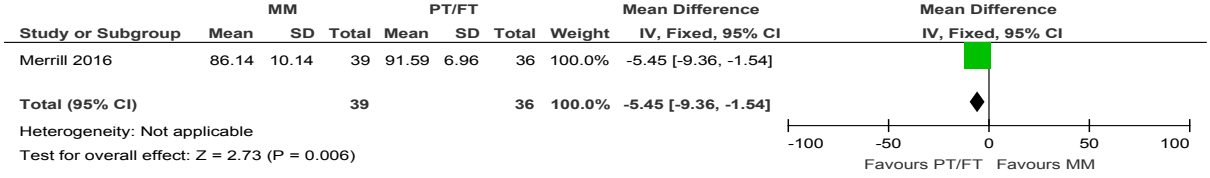


Figure 50: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

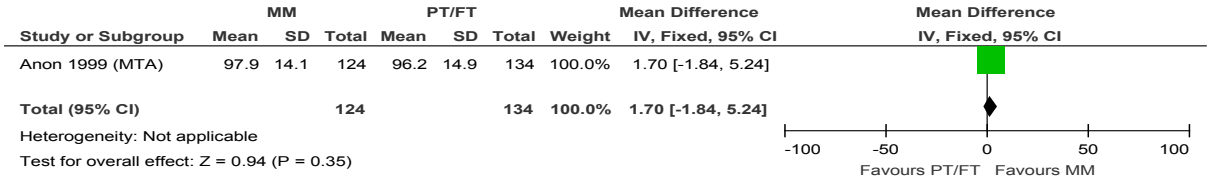
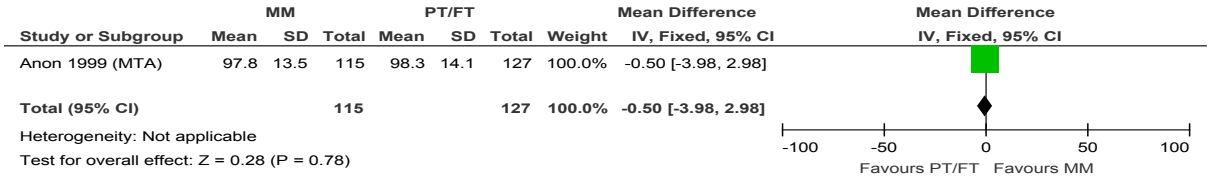


Figure 51: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)



E.1.2 Combined treatment versus non-pharmacological treatment

E.1.2.1 Atomoxetine + PT/FT versus PT/FT

Figure 52: ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

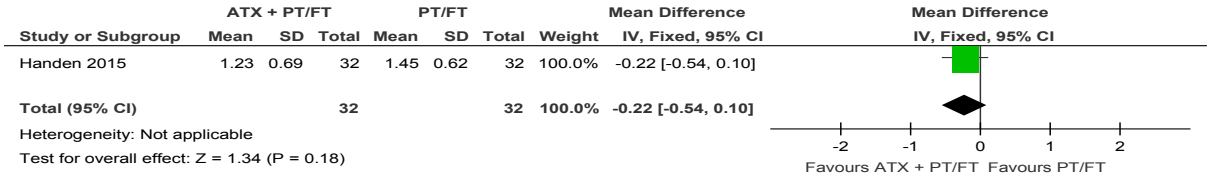


Figure 53: ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

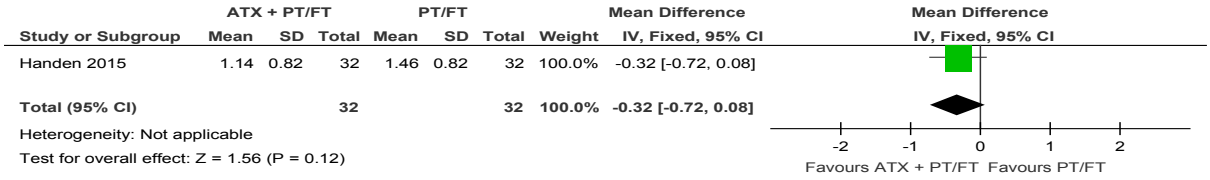


Figure 54: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

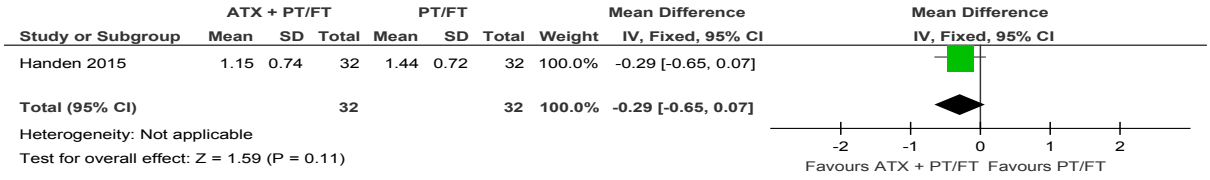


Figure 55: ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

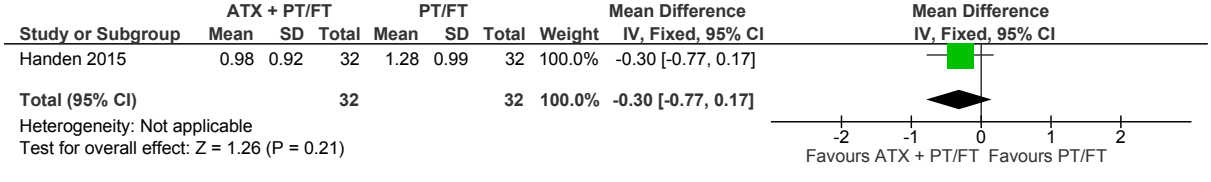


Figure 56: ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

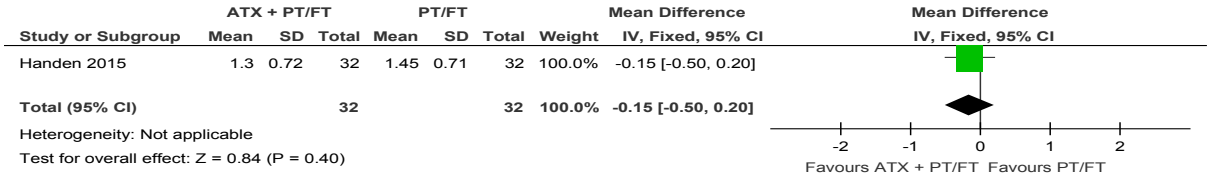


Figure 57: ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

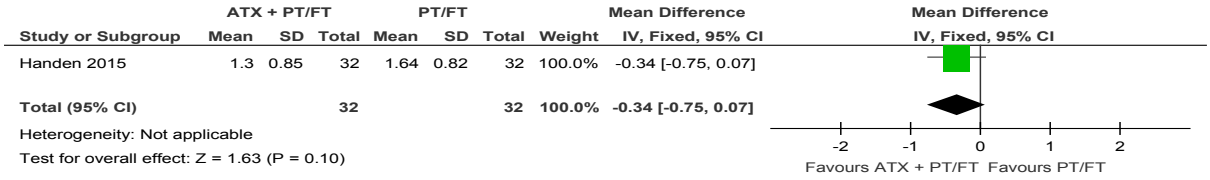
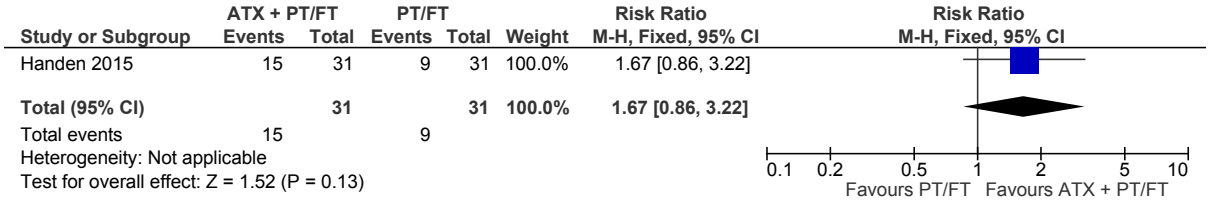


Figure 58: Responders by CGI-I (PT, <3 months)



E.1.2.2 Atomoxetine + psychoeducation versus psychoeducation

Figure 59: Quality of life (parent rated, total CHIP-CE, unclear range, high is good outcome, CS, PT <3 months)

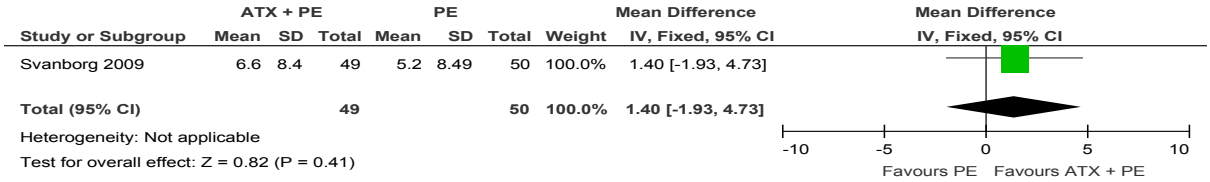


Figure 60: ADHD symptoms (total, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months)

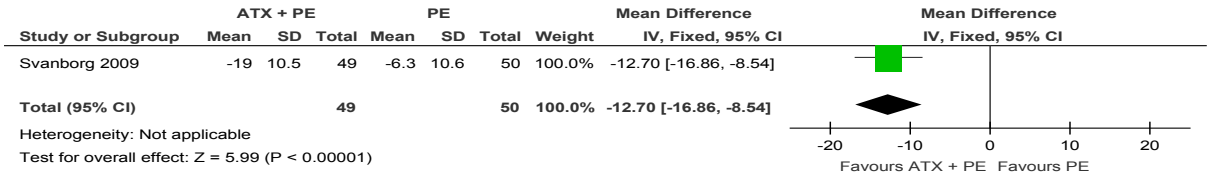


Figure 61: ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months)

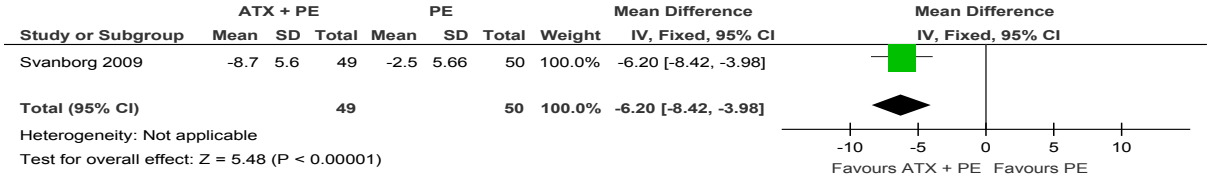


Figure 62: ADHD symptoms (inattention, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months)

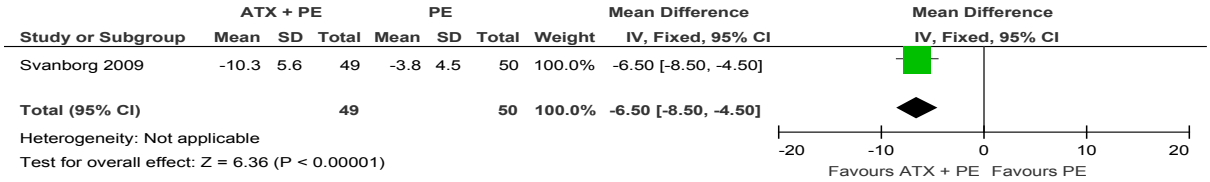
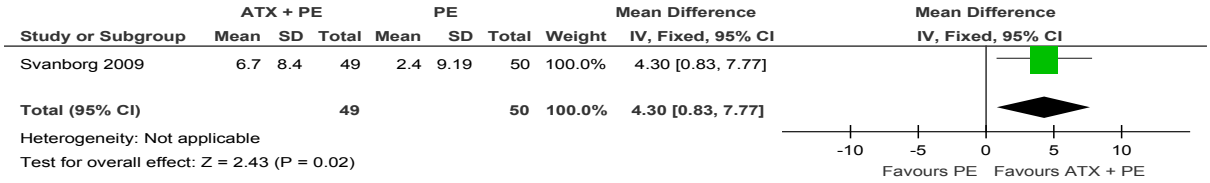


Figure 63: Academic (parent rated, academic CHIP-CE, unclear range, high is good outcome, CS, PT <3 months)



E.1.2.3 Atomoxetine + CBT versus CBT

Figure 64: ADHD symptoms (total, parent, DSM-IV checklist, 0-54, high is poor, CS, PT <3 months)

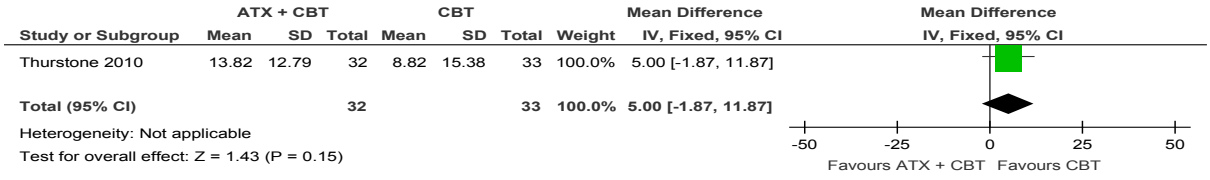


Figure 65: ADHD symptoms (total, self, DSM-IV checklist, 0-54, high is poor, CS, PT <3 months)

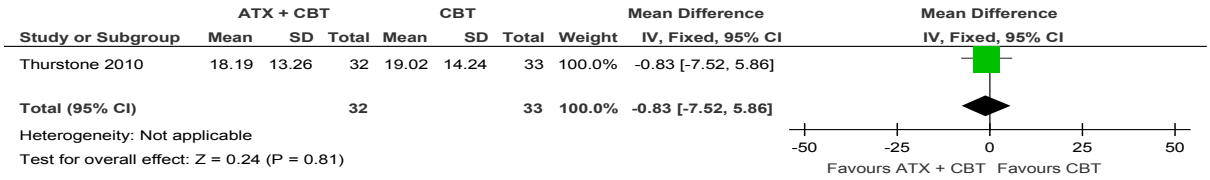
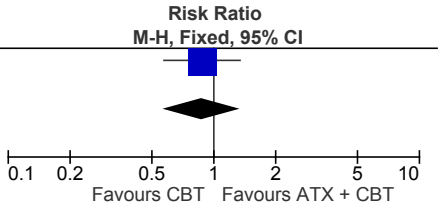


Figure 66: Responders by CGI-I (PT, <3 months)

Study or Subgroup	ATX + CBT Events	ATX + CBT Total	CBT Events	CBT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Thurstone 2010	17	32	20	33	100.0%	0.88 [0.57, 1.34]
Total (95% CI)		**32**		**33**	**100.0%**	**0.88 [0.57, 1.34]**
Total events	17		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)



E.1.2.4 Stimulants + NF versus NF

Figure 67: ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months)

Study or Subgroup	Stims + NF Mean	Stims + NF SD	Stims + NF Total	NF Mean	NF SD	NF Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	24.6	8.0341	30	23.5	8.302	30	100.0%	1.10 [-3.03, 5.23]
Total (95% CI)			**30**			**30**	**100.0%**	**1.10 [-3.03, 5.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

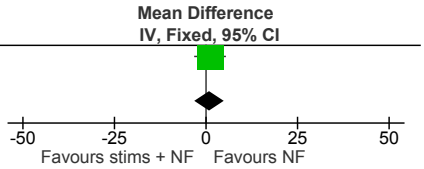


Figure 68: ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, >3 months)

Study or Subgroup	Stims + NF Mean	Stims + NF SD	Stims + NF Total	NF Mean	NF SD	NF Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	22.7	9.4642	29	23.8	8.7623	24	100.0%	-1.10 [-6.01, 3.81]
Total (95% CI)			**29**			**24**	**100.0%**	**-1.10 [-6.01, 3.81]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

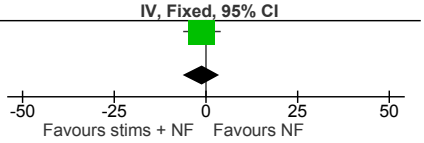


Figure 69: ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

Study or Subgroup	Stims + NF Mean	Stims + NF SD	Stims + NF Total	NF Mean	NF SD	NF Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	21.1	12.319	30	21	11.2478	30	100.0%	0.10 [-5.87, 6.07]
Total (95% CI)			**30**			**30**	**100.0%**	**0.10 [-5.87, 6.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)

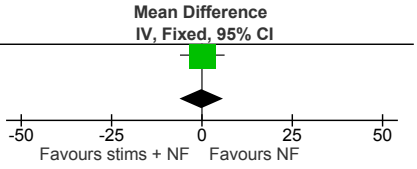


Figure 70: ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

Study or Subgroup	Stims + NF Mean	Stims + NF SD	Stims + NF Total	NF Mean	NF SD	NF Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	22.1	11.3045	29	25.3	9.236	24	100.0%	-3.20 [-8.73, 2.33]
Total (95% CI)			**29**			**24**	**100.0%**	**-3.20 [-8.73, 2.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

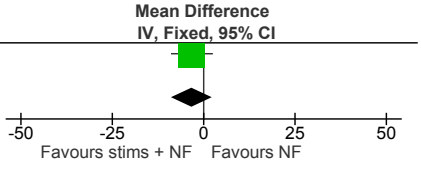


Figure 71: ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months)

Study or Subgroup	Stims + NF Mean	Stims + NF SD	Stims + NF Total	NF Mean	NF SD	NF Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	9.5	4.8205	30	9.2	5.0883	30	100.0%	0.30 [-2.21, 2.81]
Total (95% CI)			**30**			**30**	**100.0%**	**0.30 [-2.21, 2.81]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.81)

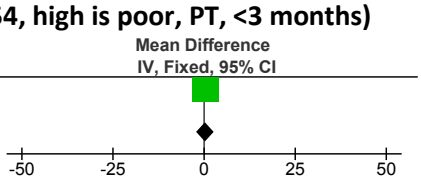


Figure 72: ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, >3 months)

Study or Subgroup	Stims + NF Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	10.9	5.5208	29	10	5.21	24	100.0%	0.90 [-2.00, 3.80]
Total (95% CI)			**29**			**24**	**100.0%**	**0.90 [-2.00, 3.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

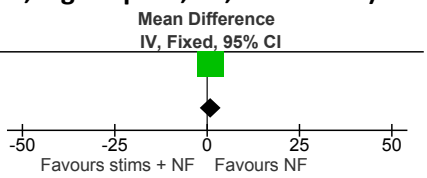


Figure 73: ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

Study or Subgroup	Stims + NF Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	8.7	8.0341	30	10.8	7.4985	30	100.0%	-2.10 [-6.03, 1.83]
Total (95% CI)			**30**			**30**	**100.0%**	**-2.10 [-6.03, 1.83]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.30)

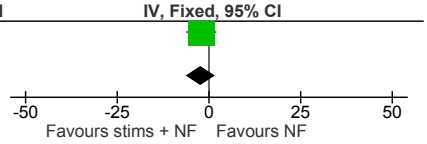


Figure 74: ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

Study or Subgroup	Stims + NF Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	10.5	6.5724	29	10.5	5.4468	24	100.0%	0.00 [-3.24, 3.24]
Total (95% CI)			**29**			**24**	**100.0%**	**0.00 [-3.24, 3.24]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

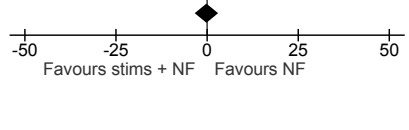


Figure 75: ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, <3 months)

Study or Subgroup	Stims + NF Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	7	2.9459	30	5.8	3.2137	30	100.0%	1.20 [-0.36, 2.76]
Total (95% CI)			**30**			**30**	**100.0%**	**1.20 [-0.36, 2.76]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)

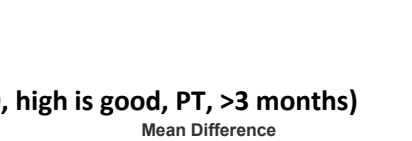


Figure 76: ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, >3 months)

Study or Subgroup	Stims + NF Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2017	5.9	2.3661	29	5.8	2.3682	24	100.0%	0.10 [-1.18, 1.38]
Total (95% CI)			**29**			**24**	**100.0%**	**0.10 [-1.18, 1.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

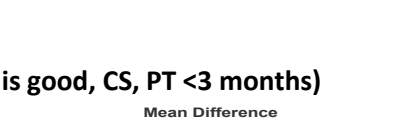


Figure 77: ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months)

Study or Subgroup	Stims + NF Mean	SD	Total	NF Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Duric 2014	1	2.9321	25	1.4	2.8418	25	100.0%	-0.40 [-2.00, 1.20]
Total (95% CI)			**25**			**25**	**100.0%**	**-0.40 [-2.00, 1.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)

Figure 78: ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months)

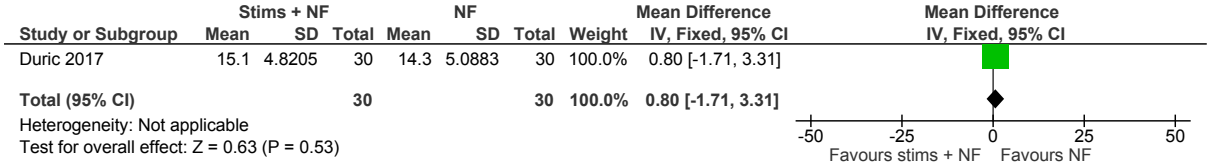


Figure 79: ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, >3 months)

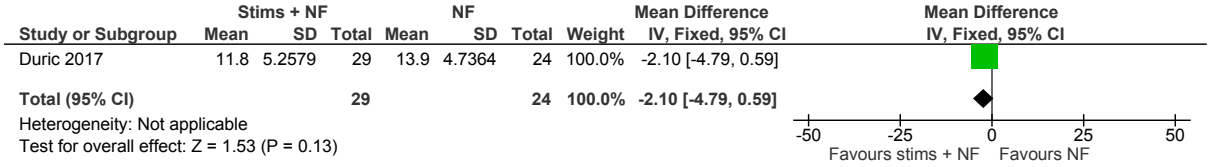


Figure 80: ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

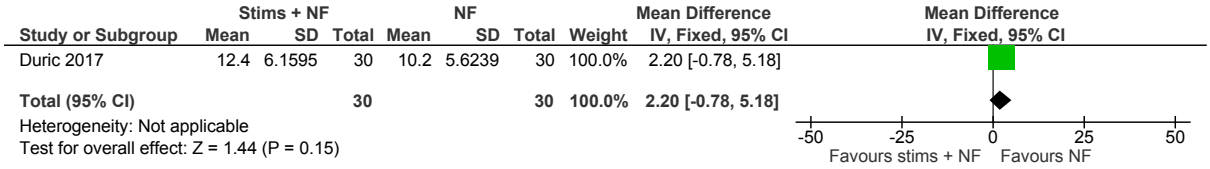


Figure 81: ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

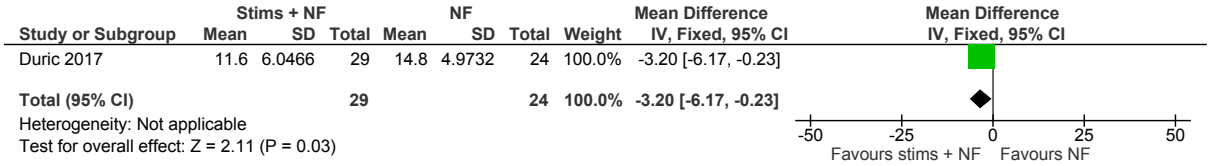


Figure 82: ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, <3 months)

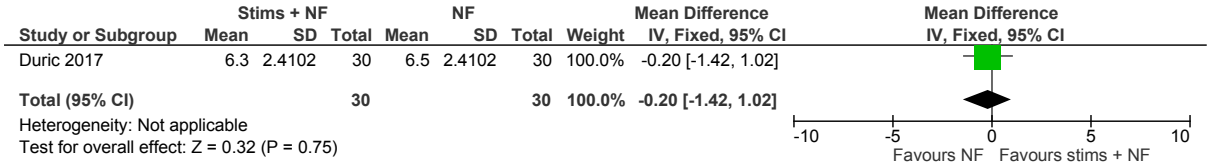


Figure 83: ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, >3 months)

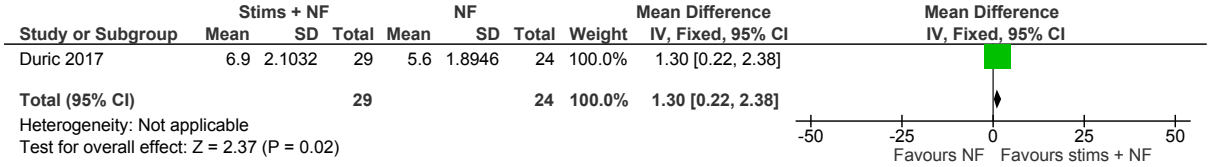


Figure 84: ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months)

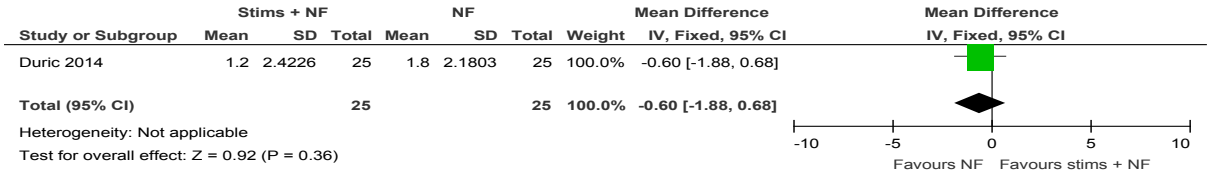


Figure 85: Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months)

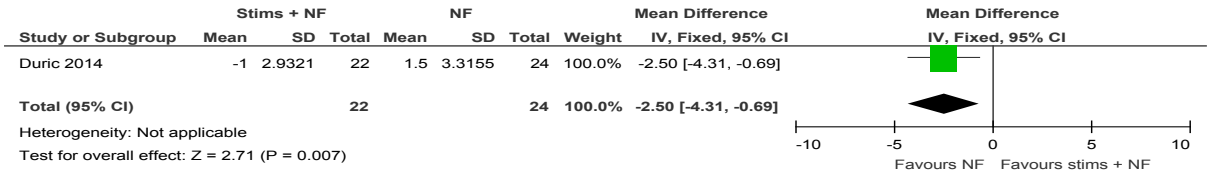


Figure 86: Academic (general, self, SRQ, 1-10, high is good, PT <3 months)

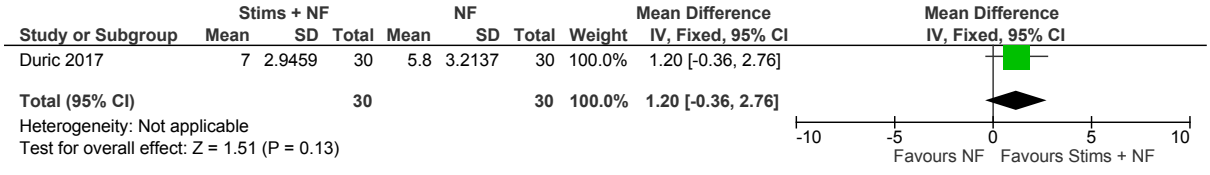
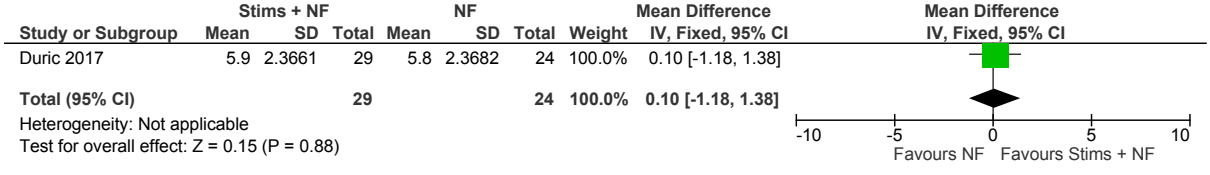
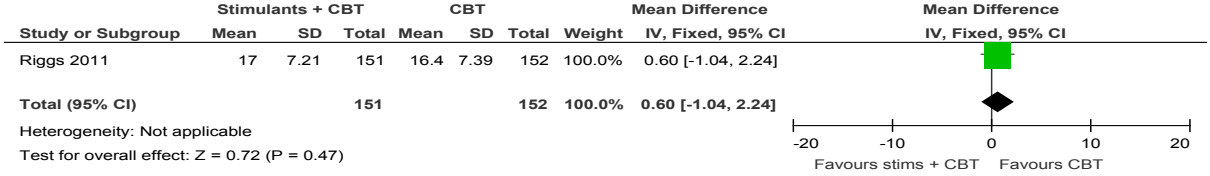


Figure 87: Academic (general, self, SRQ, 1-10, high is good, PT >3 months)



E.1.2.5 Stimulants + CBT versus CBT

Figure 88: ADHD symptoms (total, observer, ADHD-RS, 0-68, high is poor, FV, PT, >3 months)



E.1.2.6 Mixed medication + PT/FT versus PT/FT

Figure 89: ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)

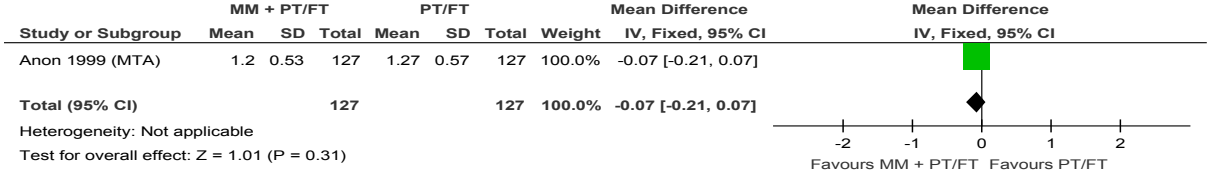


Figure 90: ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months)

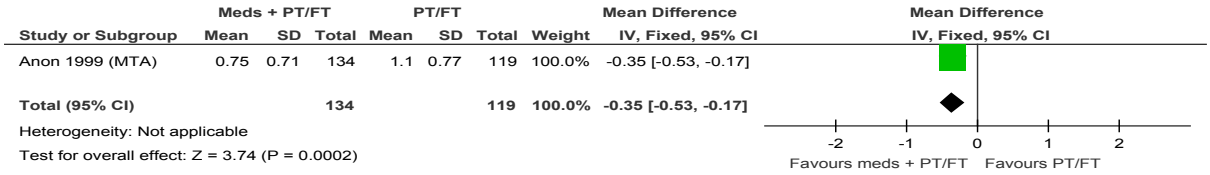


Figure 91: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

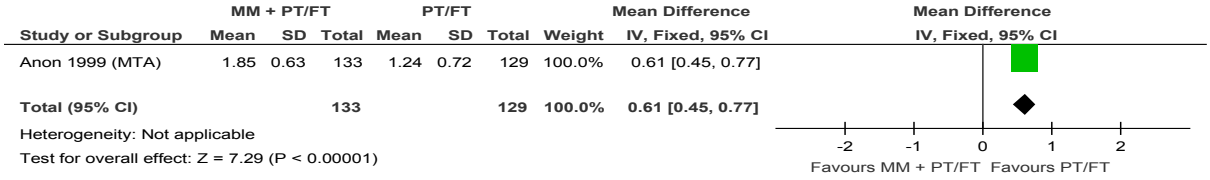


Figure 92: ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)

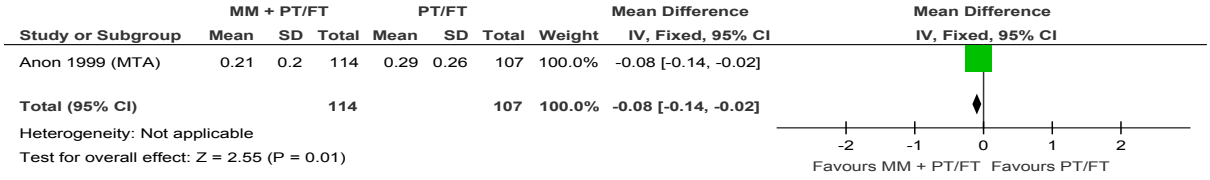


Figure 93: ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

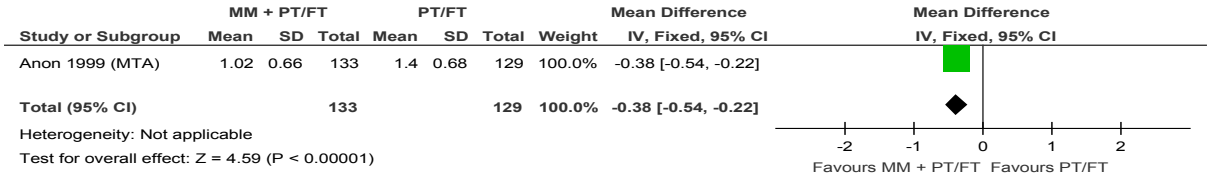


Figure 94: ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)

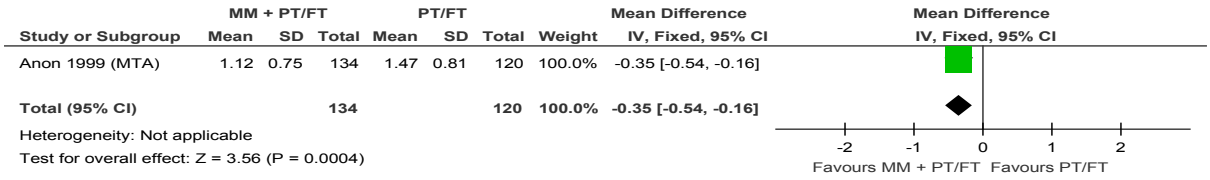


Figure 95: Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)

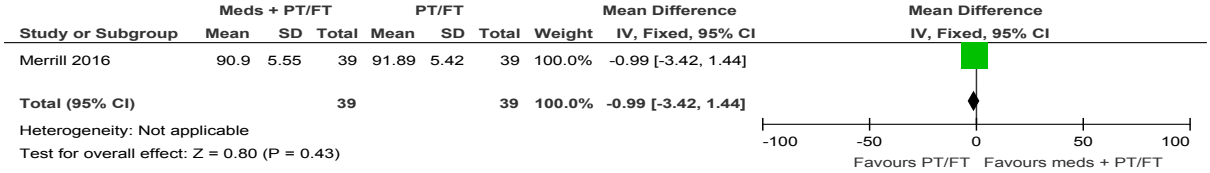


Figure 96: Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

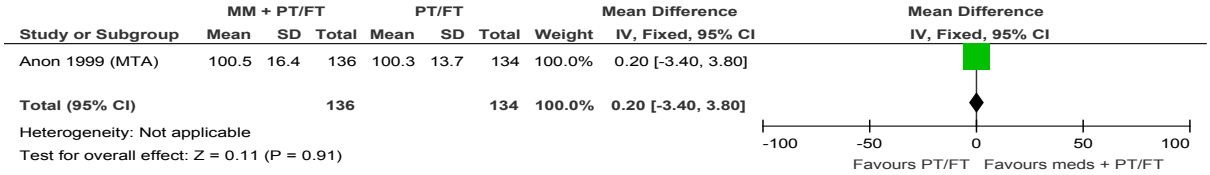


Figure 97: Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)

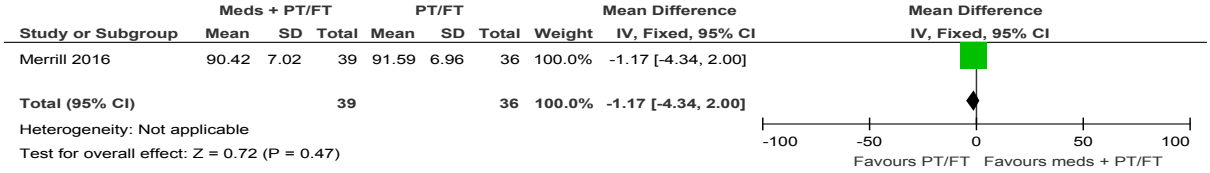


Figure 98: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

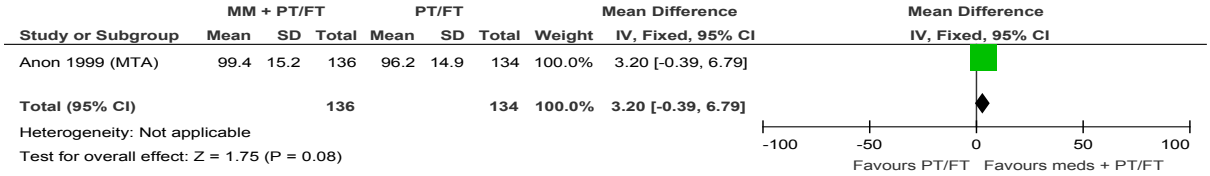
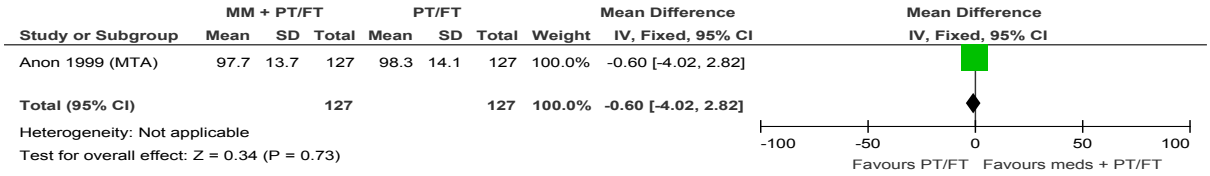


Figure 99: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)



E.1.3 Combined treatment versus pharmacological treatment

E.1.3.1 Atomoxetine + parent/family training versus atomoxetine

Figure 100: ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

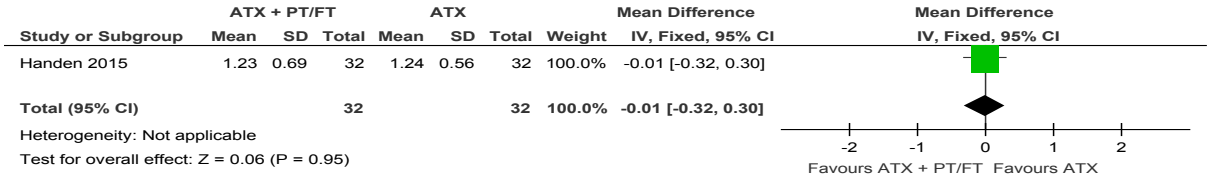


Figure 101: ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

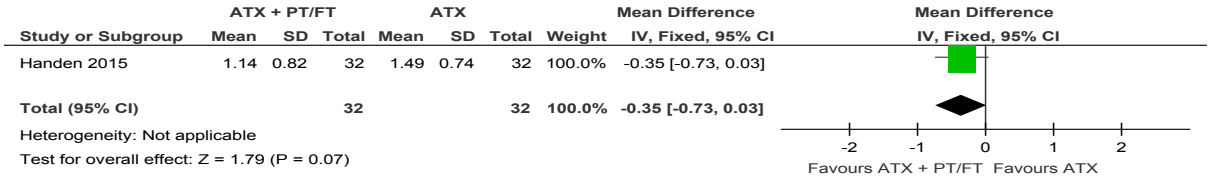


Figure 102: ADHD symptoms (hyperactivity, parent, multiple scales, higher is worse, FV, PT <3 months)

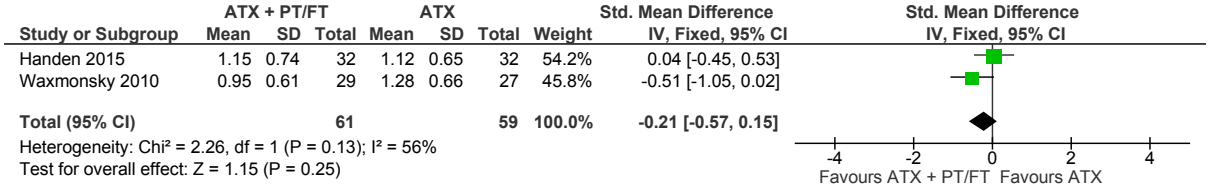


Figure 103: ADHD symptoms (hyperactivity, teacher, multiple scales, higher is worse, FV, PT <3 months)

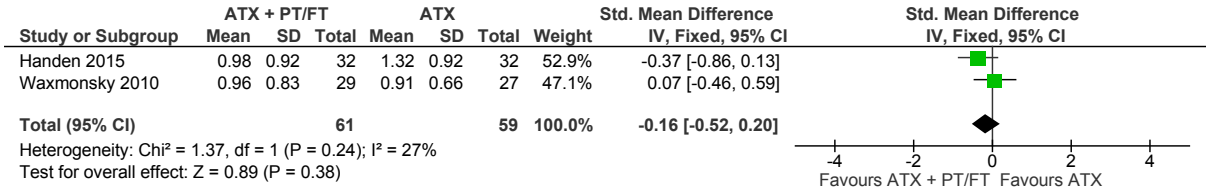


Figure 104: ADHD symptoms (inattention, parent, multiple scales, higher is worse, FV, PT <3 months)

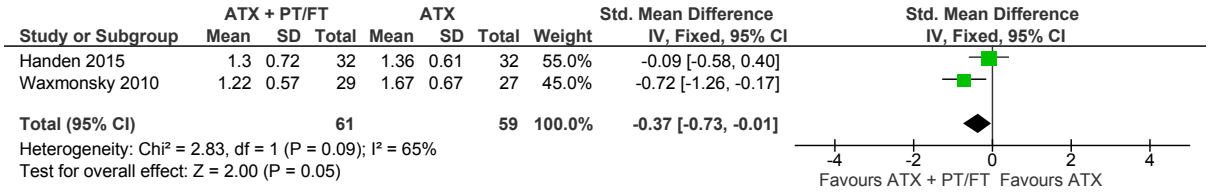


Figure 105: ADHD symptoms (inattention, teacher, multiple scales, higher is worse, FV, PT <3 months)

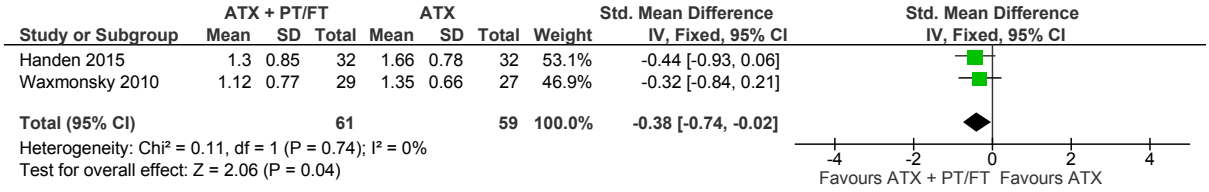


Figure 106: Responders by CGI-I (PT, <3 months)

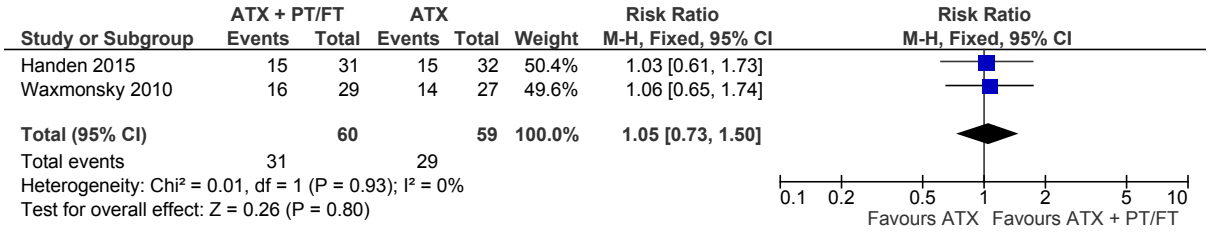
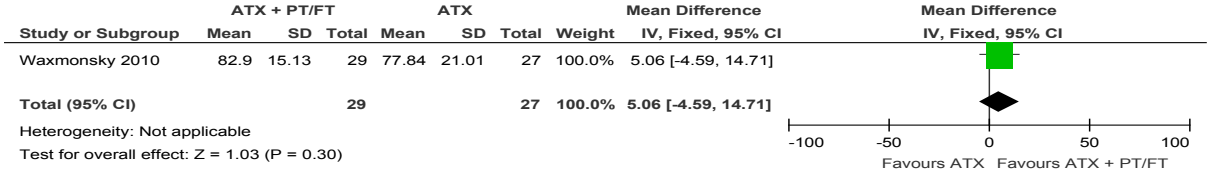


Figure 107: Behaviour/function (behaviour, 0-100, high is good, teacher, PT, <3 months)



E.1.3.2 Stimulants + PT/FT versus stimulants

Figure 108: ADHD symptoms (total, parent, multiple scales, high is poor, FV, PT, >3 months)

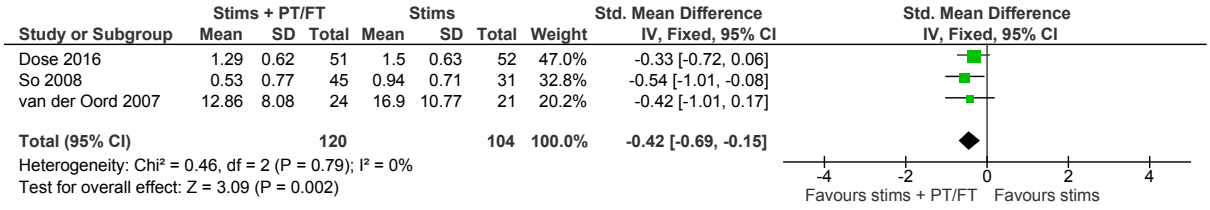


Figure 109: ADHD symptoms (total, parent, SWAN, 0-3, high is poor, FV, FU, >3 months)

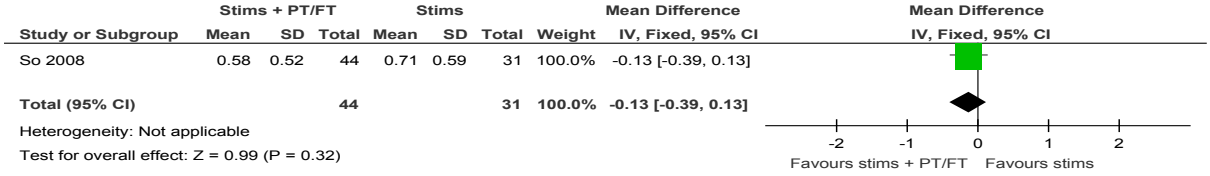


Figure 110: ADHD symptoms (total, teacher, DBDRS, 0-54, high is poor, FV, PT, <3 months)

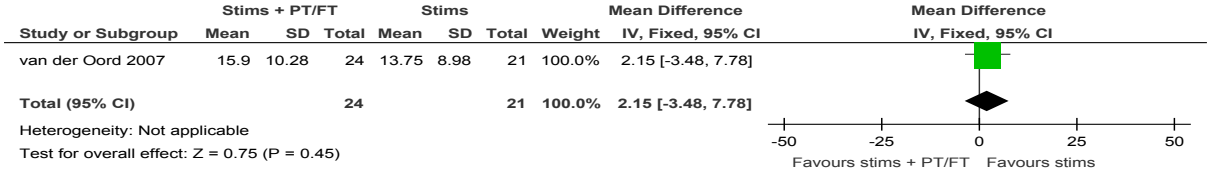


Figure 111: ADHD symptoms (hyperactivity, parent, multiple scales, 0-3, high is poor, FV, PT, >3 months)

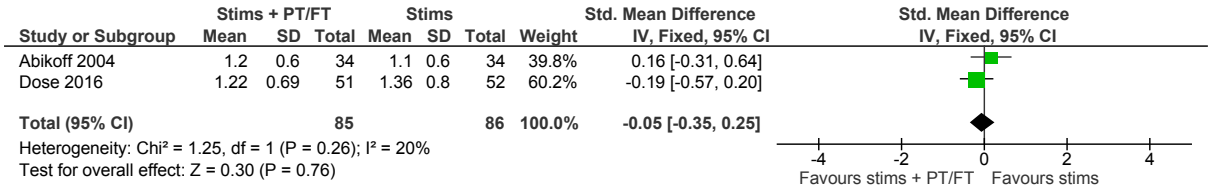


Figure 112: ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months)

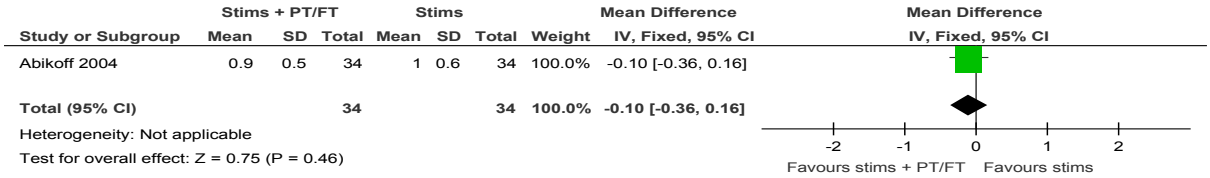


Figure 113: ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months)

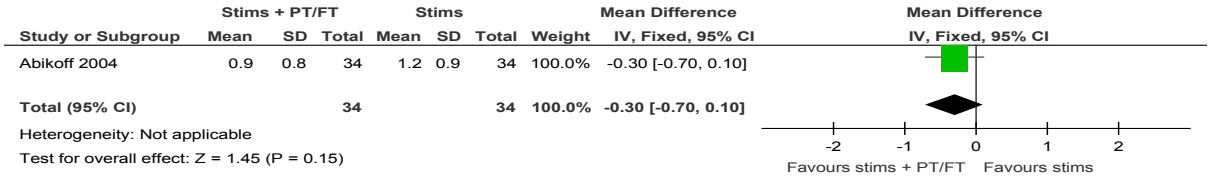


Figure 114: ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months)

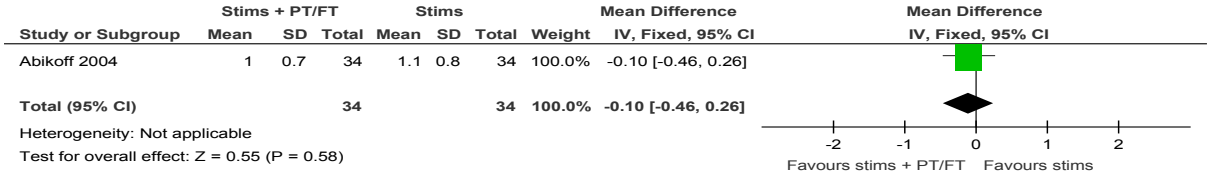


Figure 115: ADHD symptoms (inattention, parent, FBB-ADHS, 0-3, high is poor, FV, PT, >3 months)

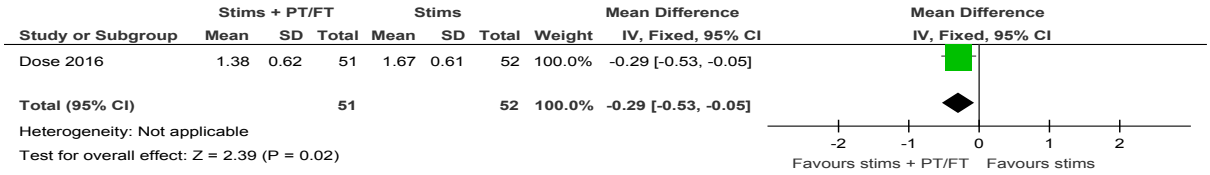
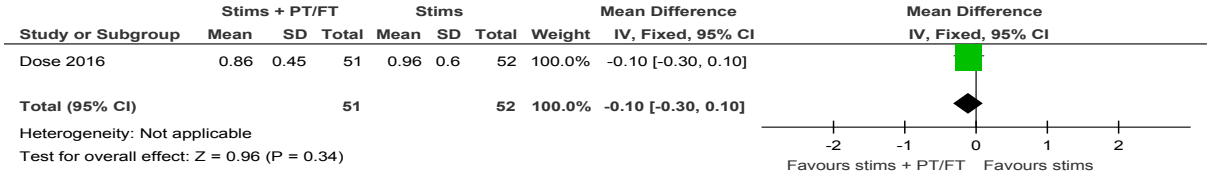


Figure 116: Behaviour/function (function, parent, WFIRS-P, 0-3, high is poor, FV, PT, >3 months)



E.1.3.3 Stimulants + PT/FT versus stimulants + NSST

Figure 117: ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, PT >3 months)

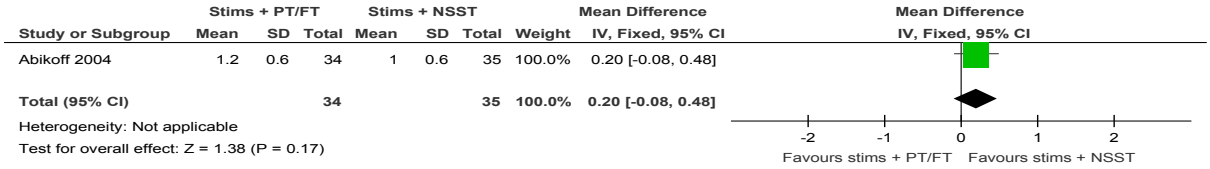


Figure 118: ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months)

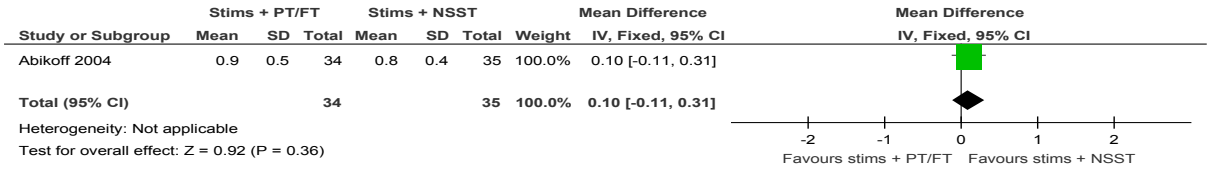


Figure 119: ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months)

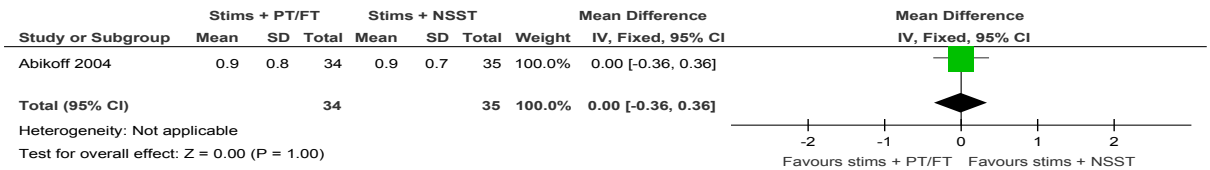
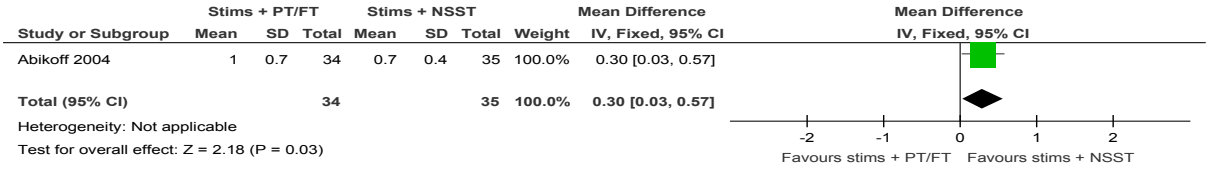
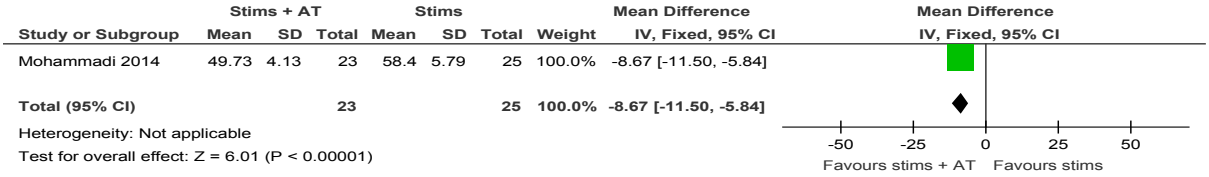


Figure 120: ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months)



E.1.3.4 Stimulants + attention/memory/cognitive training versus stimulants

Figure 121: ADHD symptoms (total, parent, Conners 48, 0-70, high is poor, FV, <3 months PT)



E.1.3.5 Stimulants + NF versus stimulants

Figure 122: ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months)

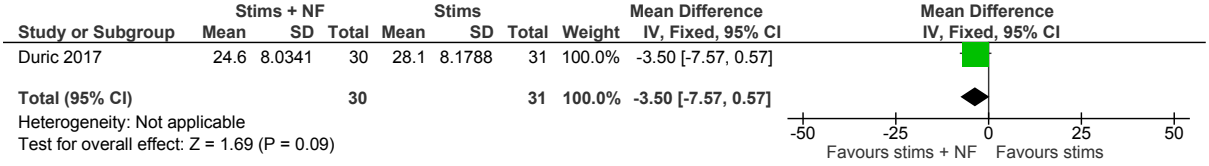


Figure 123: ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, >3 months)

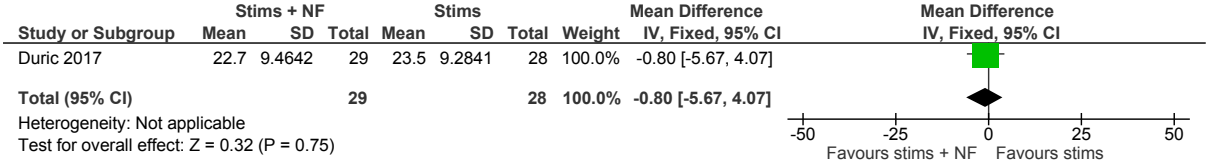


Figure 124: ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

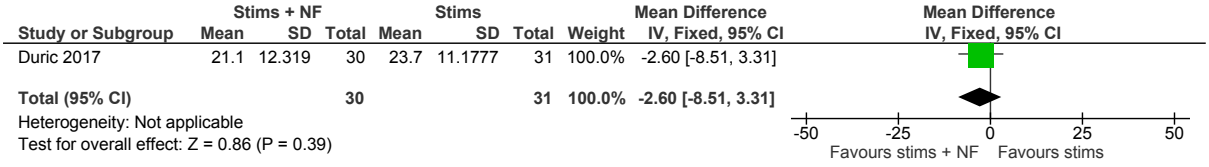


Figure 125: ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

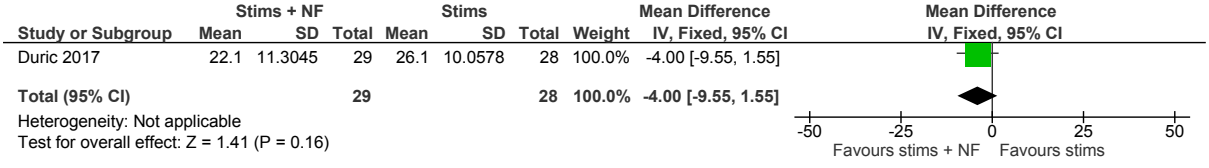


Figure 126: ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months)

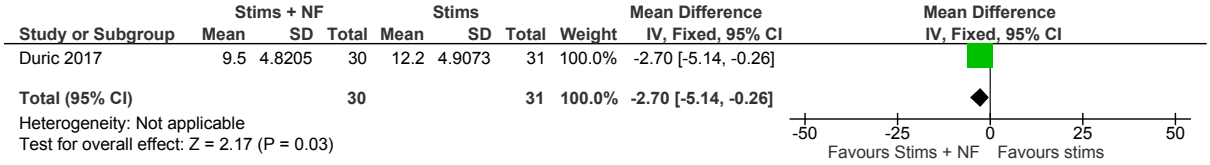


Figure 127: ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, >3 months)

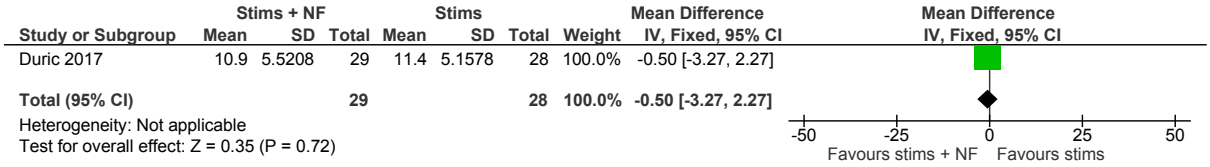


Figure 128: ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

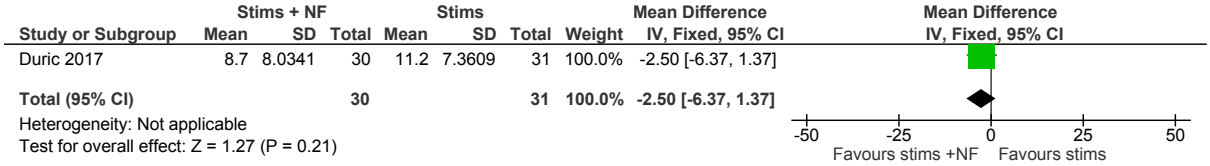


Figure 129: ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

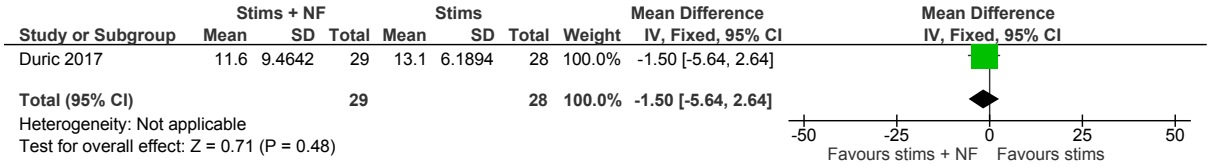


Figure 130: ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, <3 months)

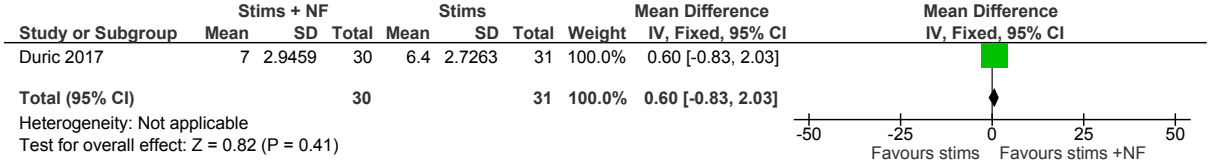


Figure 131: ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is good, PT, >3 months)

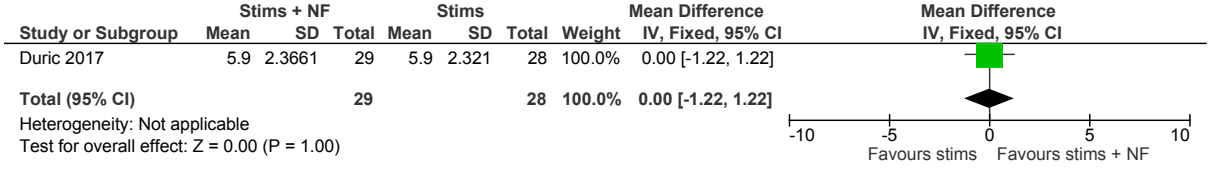


Figure 132: ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months)

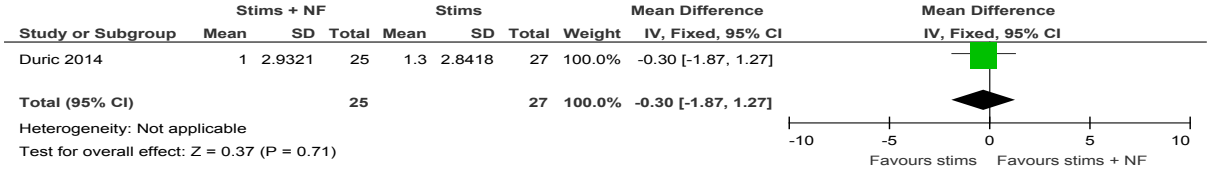


Figure 133: ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months)

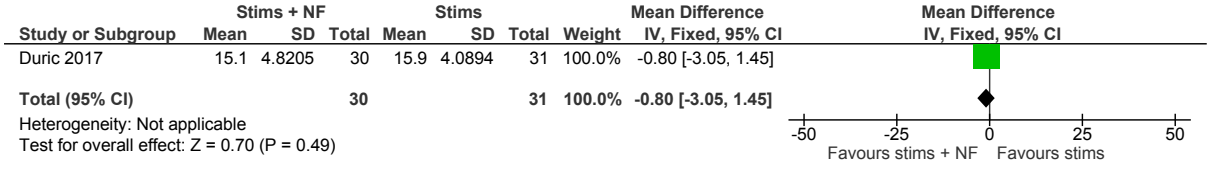


Figure 134: ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, >3 months)

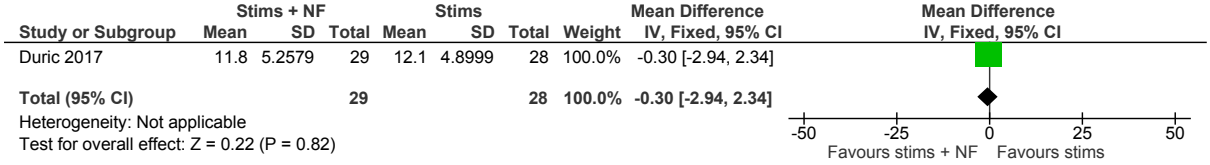


Figure 135: ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months)

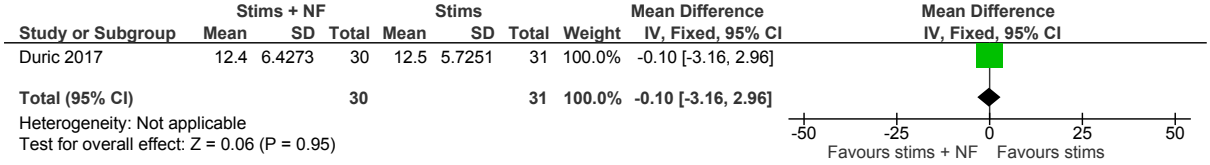


Figure 136: ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, >3 months)

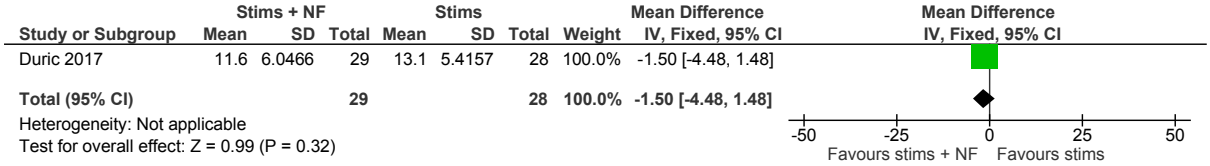


Figure 137: ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, <3 months)

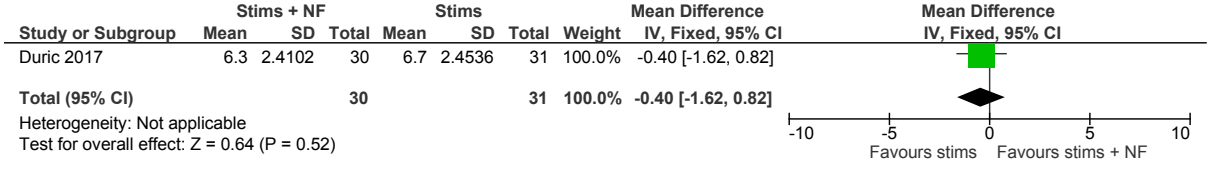


Figure 138: ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is good, PT, >3 months)

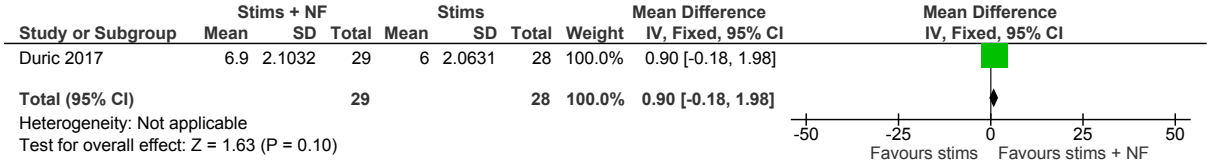


Figure 139: ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months)

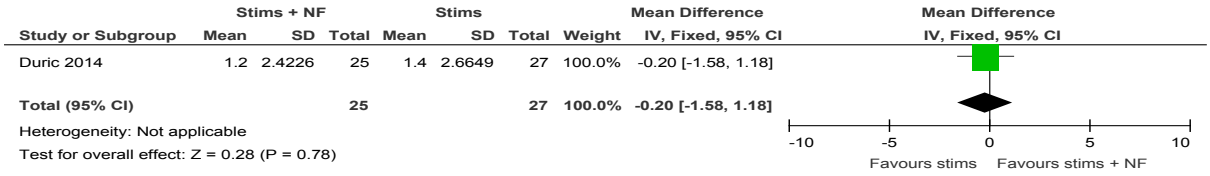


Figure 140: Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months)

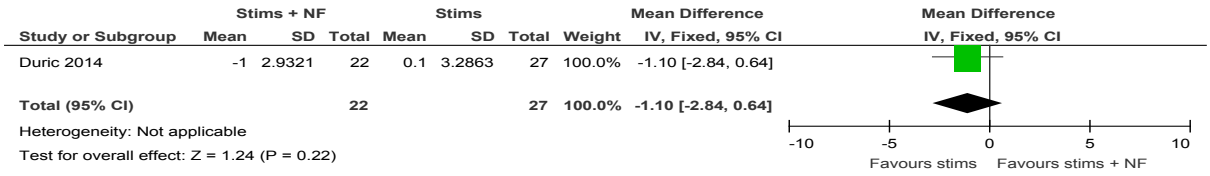


Figure 141: Academic (general, self, SRQ, 1-10, high is good, PT <3 months)

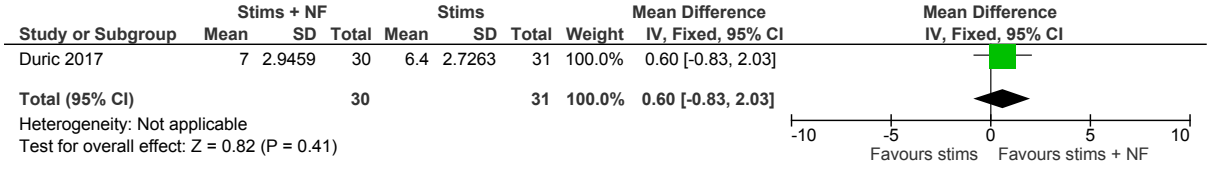
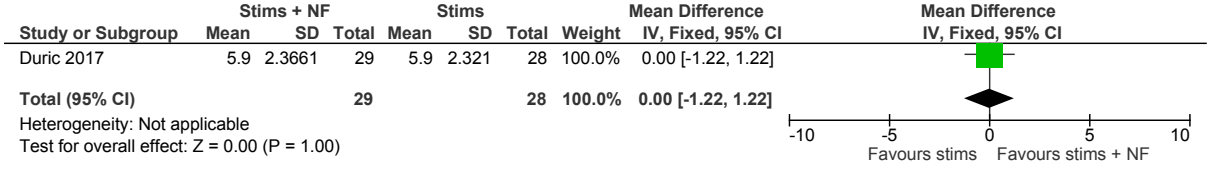


Figure 142: Academic (general, self, SRQ, 1-10, high is good, PT >3 months)



E.1.3.6 Mixed medication + PT/FT versus mixed medication

Figure 143: ADHD symptoms (total, parent, ADHD-RS-IV,0-54, high is poor, CS, FU, >3 months)

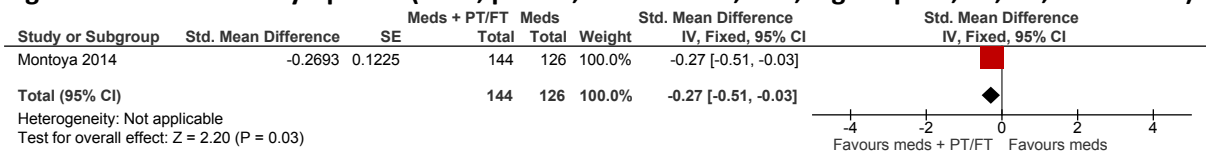


Figure 144: ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)

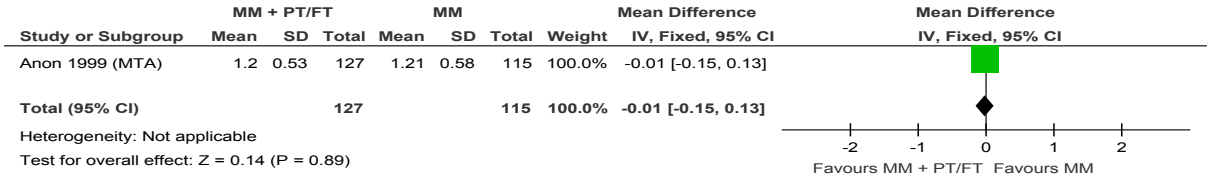


Figure 145: ADHD symptoms (hyperactivity, teacher, Conner's, 0-20, high is poor, FV, PT, <3 months)

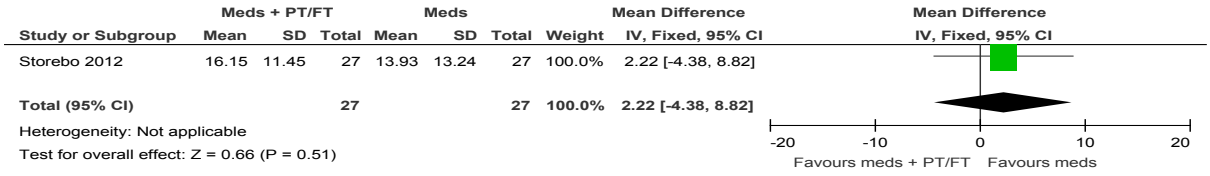


Figure 146: ADHD symptoms (hyperactivity, teacher, multiple scales, high is poor, FV, PT, >3 months)

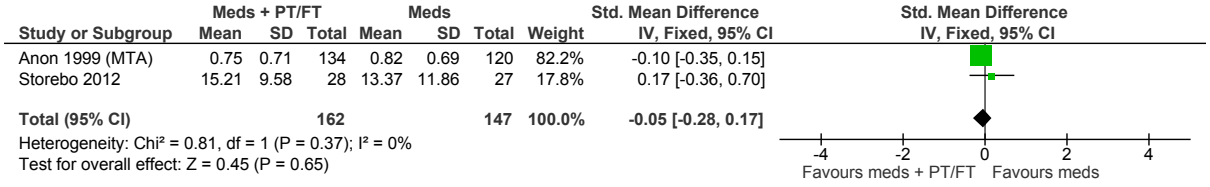


Figure 147: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

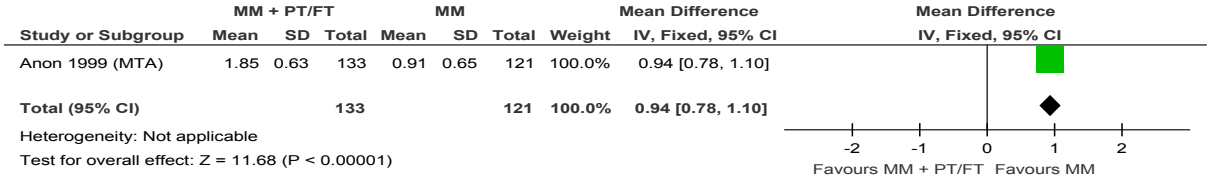


Figure 148: ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)

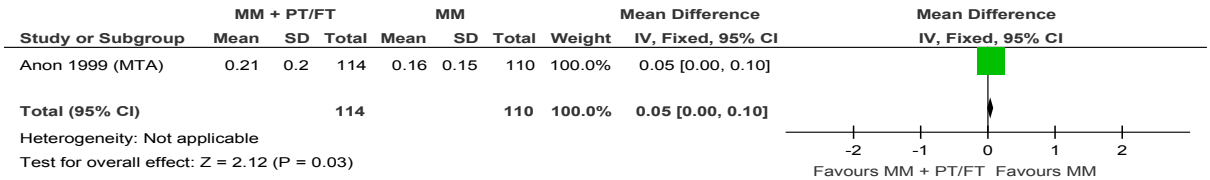


Figure 149: ADHD symptoms (hyperactivity, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months)

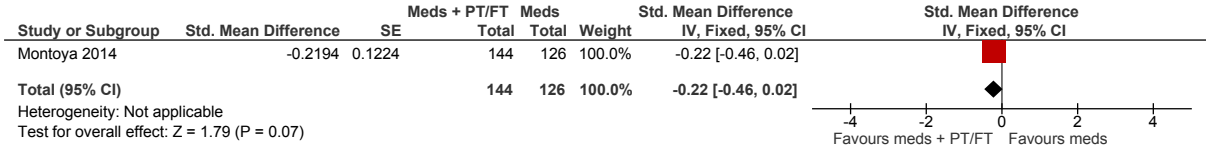


Figure 150: ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

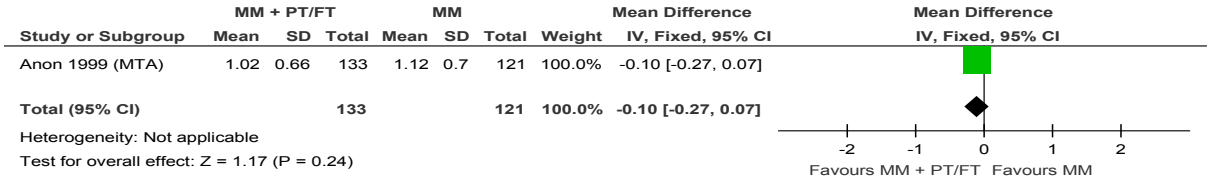


Figure 151: ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)

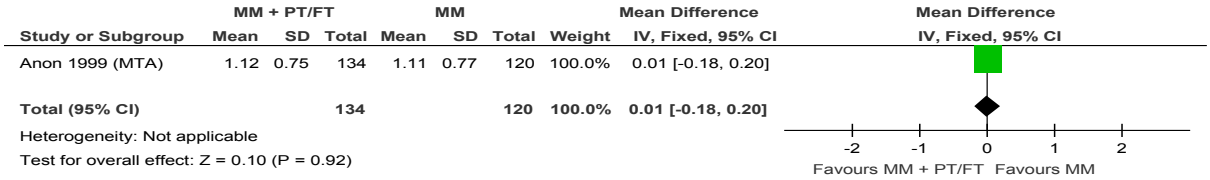


Figure 152: ADHD symptoms (inattention, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months)

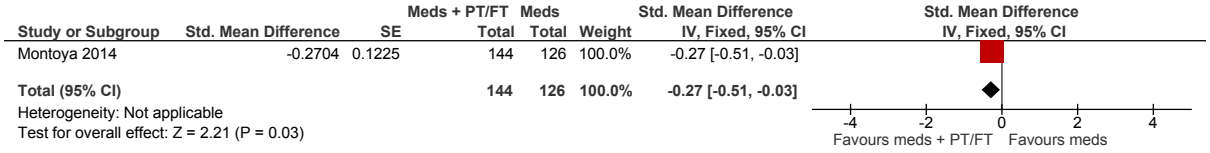


Figure 153: Behaviour/function (CBRS aggressive behaviour subscale, 0-15, high is poor, teacher, PT <3 months)

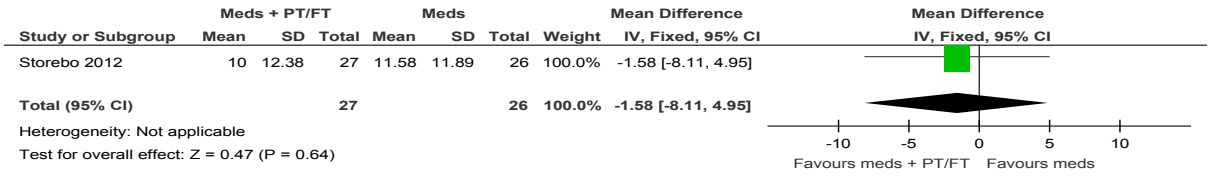


Figure 154: Behaviour/function (CBRS aggressive behaviour subscale, 0-15, high is poor, teacher, PT >3 months)

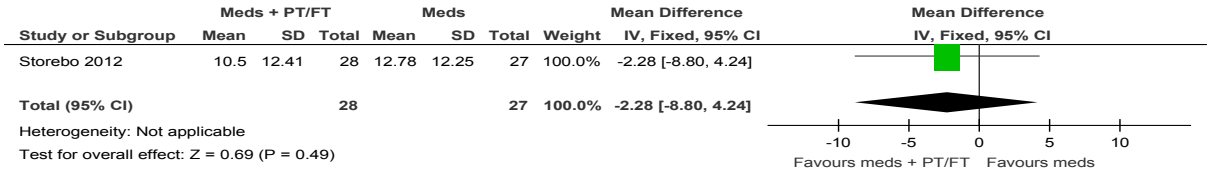


Figure 155: Emotional dysregulation (CBRS emotional distress subscale, 0-20, high is poor, teacher, PT <3 months)

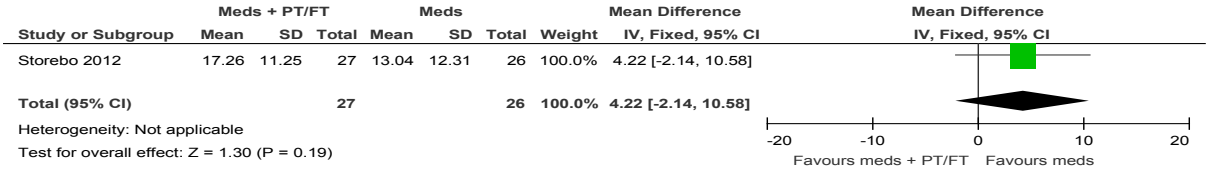


Figure 156: Emotional dysregulation (CBRS emotional distress subscale, 0-20, high is poor, teacher, PT >3 months)

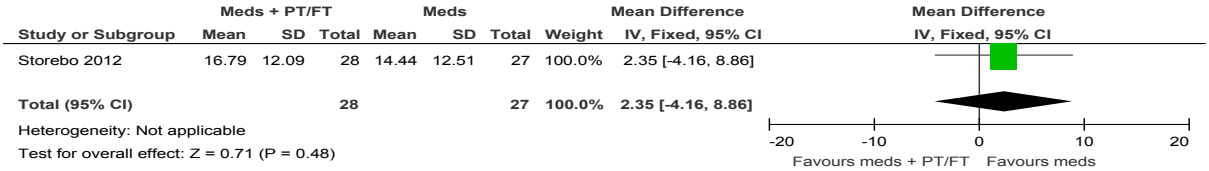


Figure 157: Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)

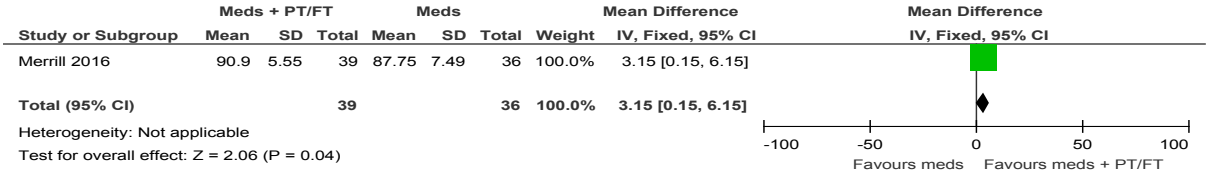


Figure 158: Academic outcomes (maths accuracy , observer, WIAT, 0-132, high is better, PT >3 months)

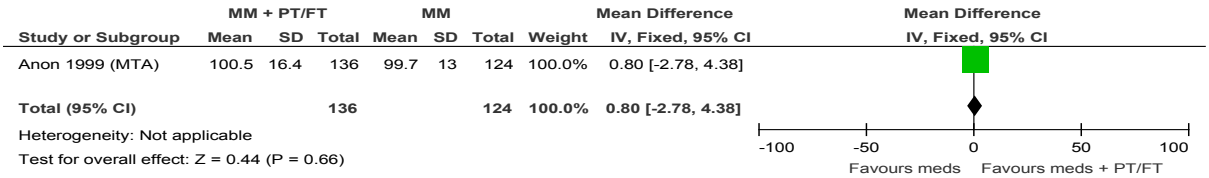


Figure 159: Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)

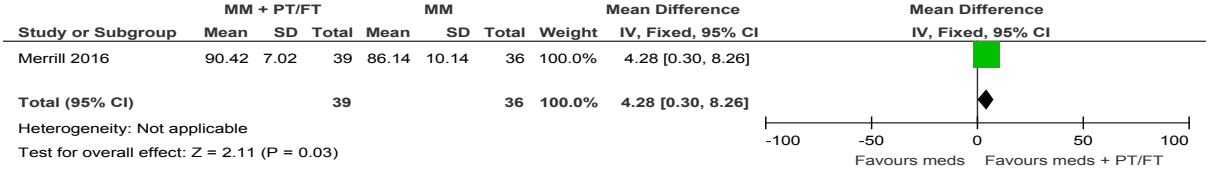


Figure 160: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

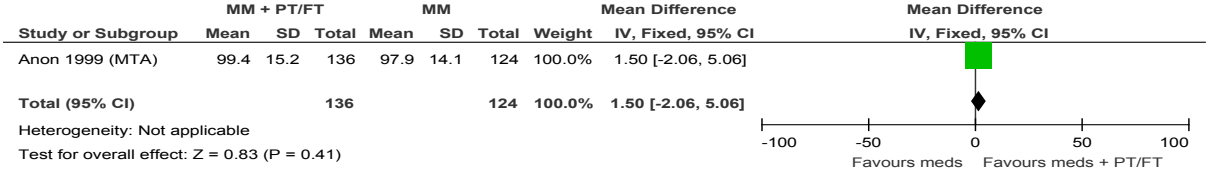


Figure 161: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)

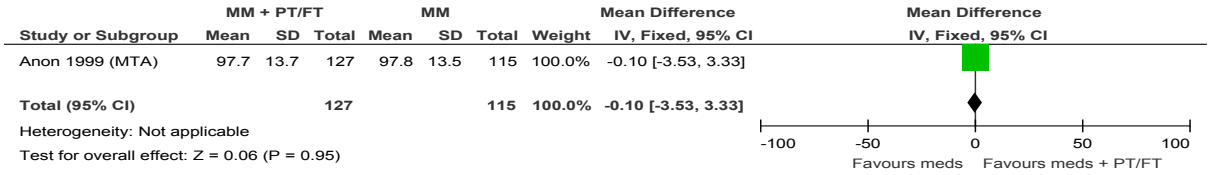


Figure 162: Academic outcomes (general, CBRS academic subscale, 0-30, high is poor, teacher, PT <3 months)

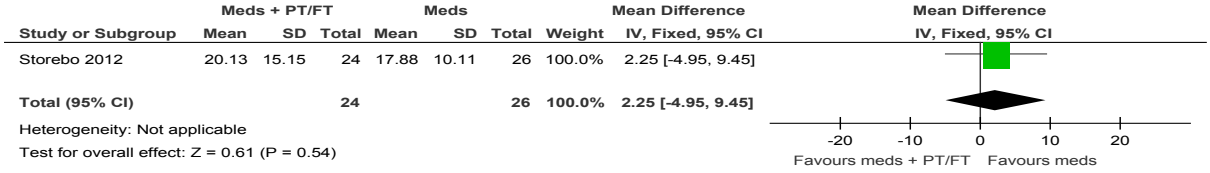
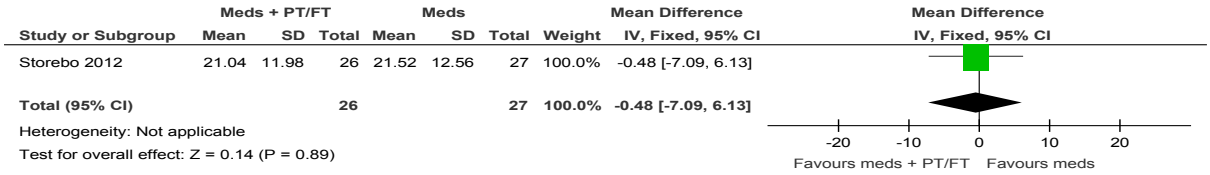


Figure 163: Academic outcomes (general, CBRS academic subscale, 0-30, high is poor, teacher, PT >3 months)



E.1.3.7 Mixed medication + CBT versus mixed medication

Figure 164: ADHD symptoms (total, self, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

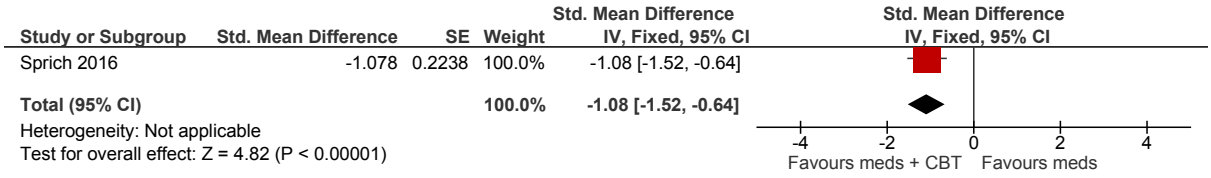


Figure 165: ADHD symptoms (total, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months)

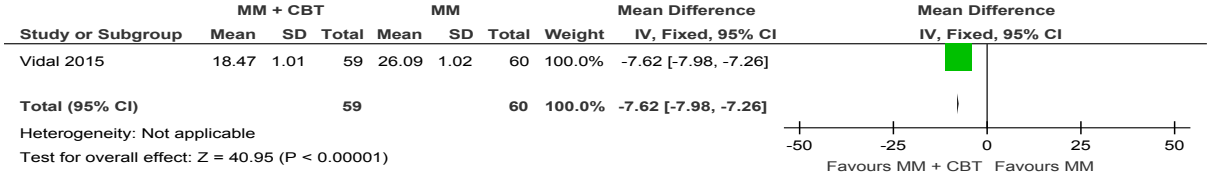


Figure 166: ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months)

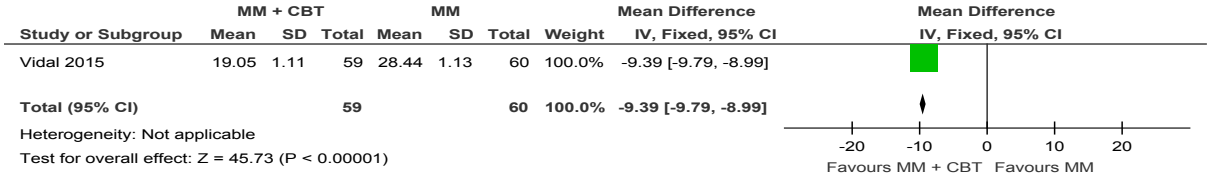


Figure 167: ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

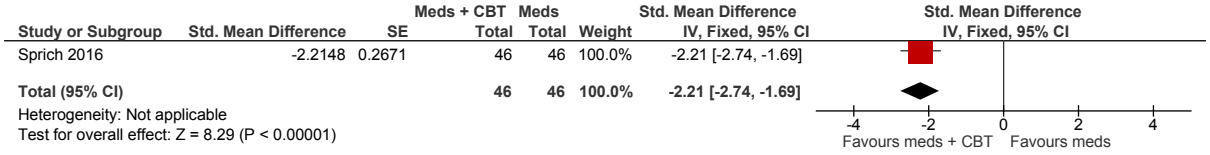


Figure 168: ADHD symptoms (hyperactivity, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months)

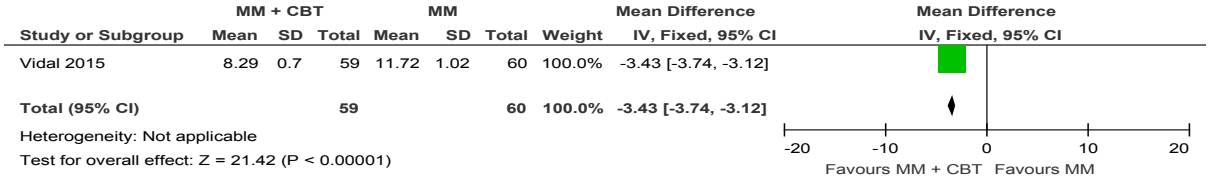


Figure 169: ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months)

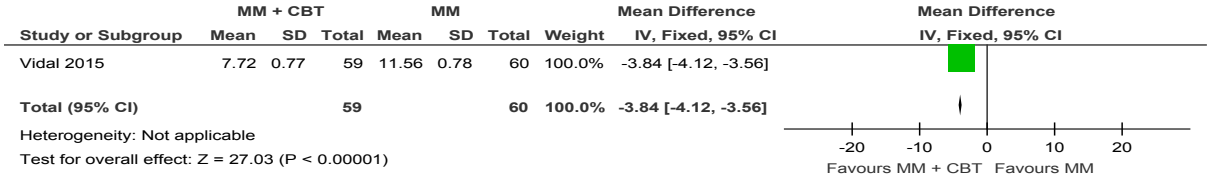


Figure 170: ADHD symptoms (inattention, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months)

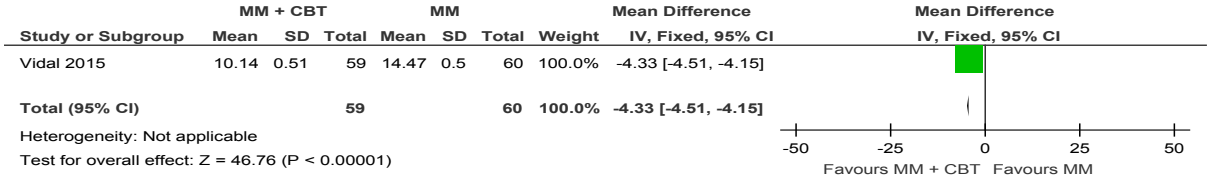
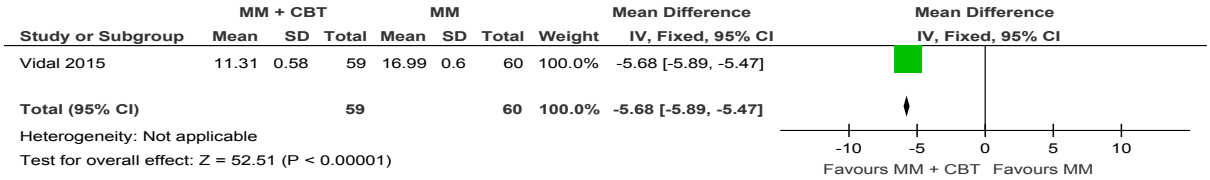


Figure 171: ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months)



E.1.3.8 Mixed medication + PE versus mixed medication + NSST

Figure 172: ADHD symptoms (hyperactivity, parent, CPRS, 0-27, high is poor, FV, PT <3 months)

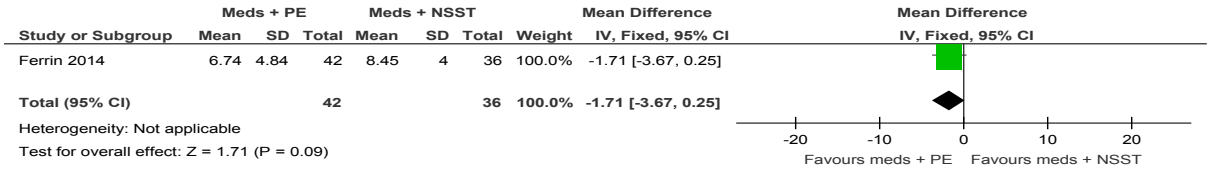


Figure 173: ADHD symptoms (hyperactivity, parent, CPRS, 0-27, high is poor, FV, FU >3 months)

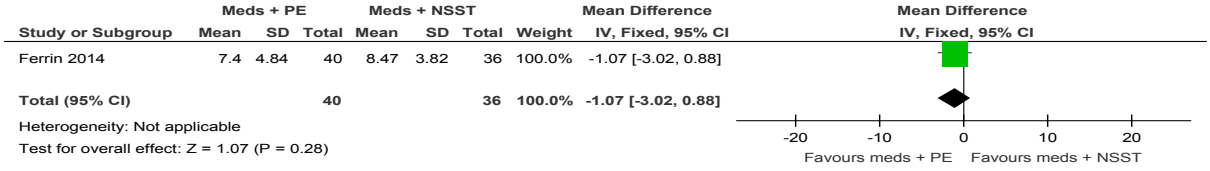


Figure 174: ADHD symptoms (inattention, parent, CPRS, 0-27, high is poor, FV, PT <3 months)

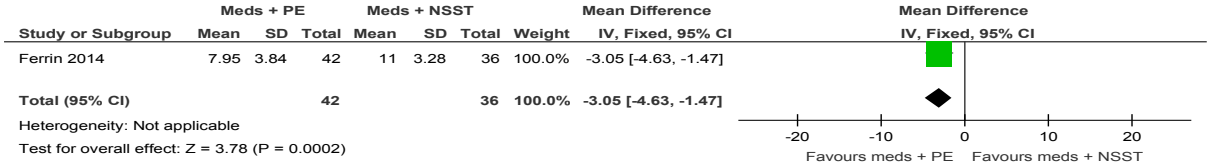


Figure 175: ADHD symptoms (inattention, parent, CPRS, 0-27, high is poor, FV, FU >3 months)

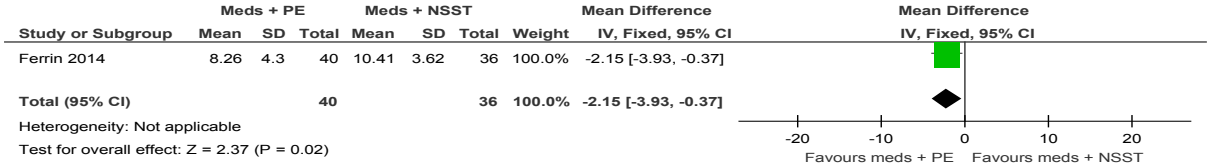


Figure 176: Behaviour/function (opposition, parent, CPRS, 0-27, high is poor, FV, PT <3 months)

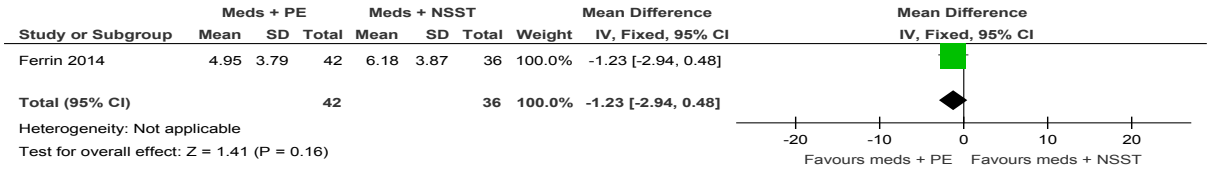


Figure 177: Behaviour/function (opposition, parent, CPRS, 0-27, high is poor, FV, FU >3 months)

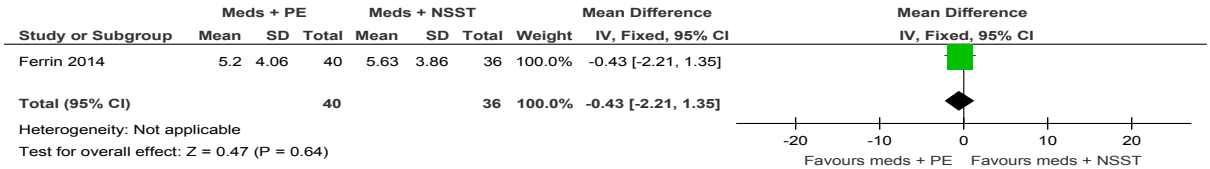


Figure 178: Emotional dysregulation (SDQ, parent, 0-25, high is poor, FV, PT <3 months)

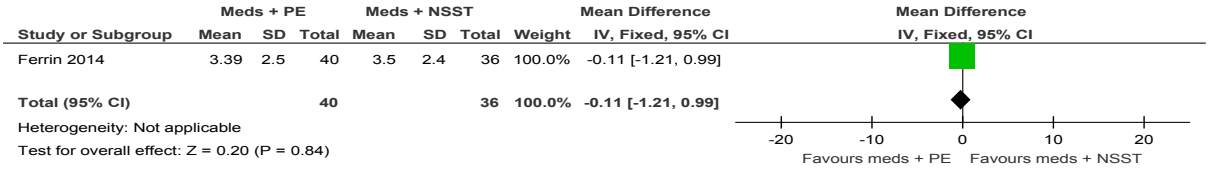
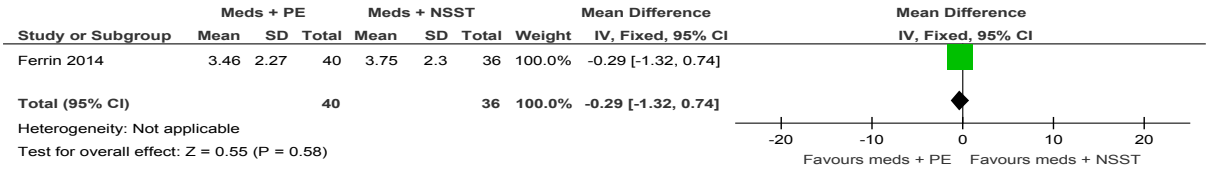


Figure 179: Emotional dysregulation (SDQ, parent, 0-25, high is poor, FV, FU >3 months)



E.1.3.9 Mixed medication + sleep intervention versus mixed medication

Figure 180: ADHD symptoms (total, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months)

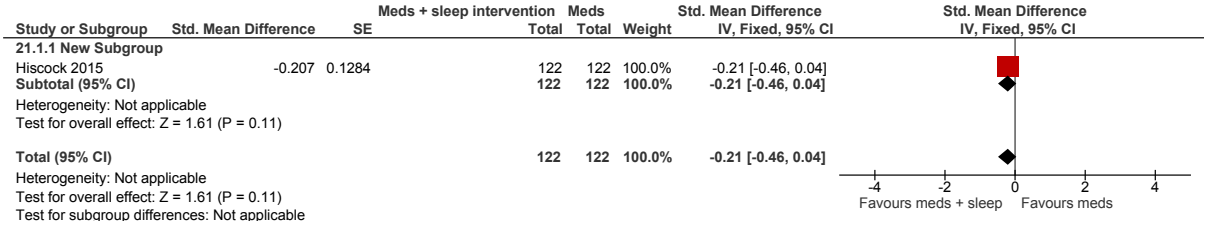


Figure 181: ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months)

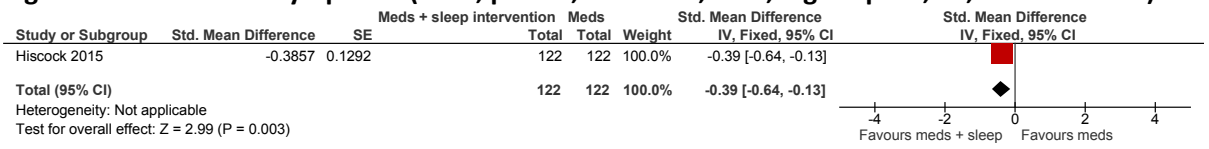


Figure 182: ADHD symptoms (total, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

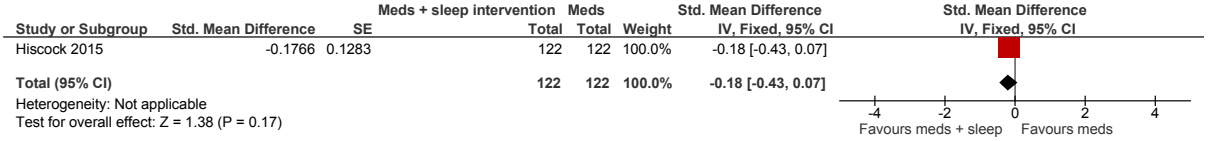


Figure 183: ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

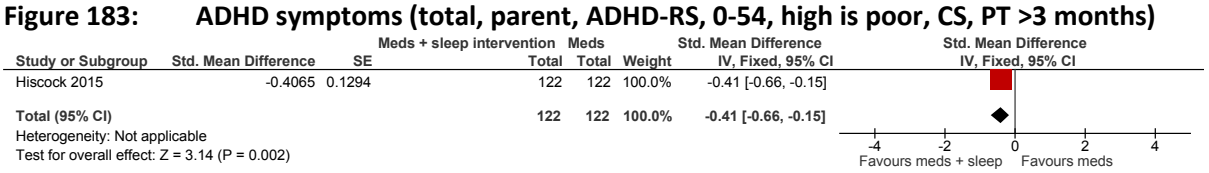


Figure 184: ADHD symptoms (hyperactivity, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months)

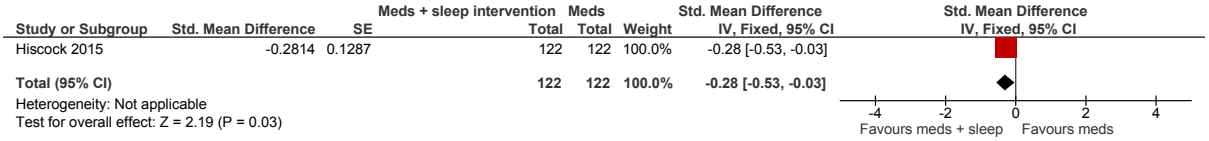


Figure 185: ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months)

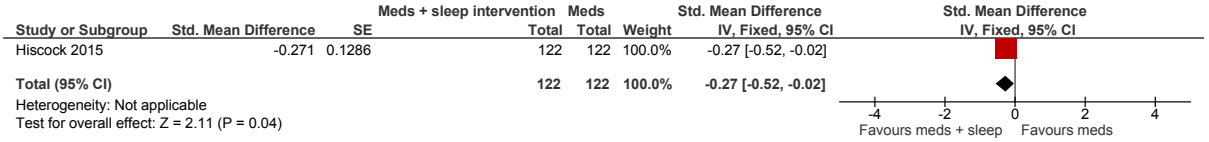


Figure 186: ADHD symptoms (hyperactivity, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

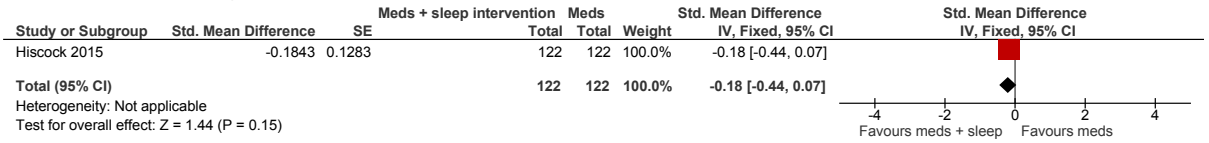


Figure 187: ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

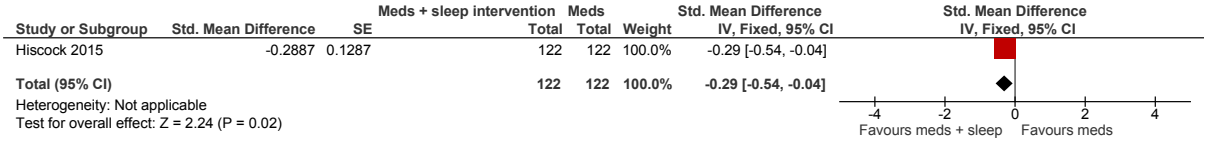


Figure 188: ADHD symptoms (inattention, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months)

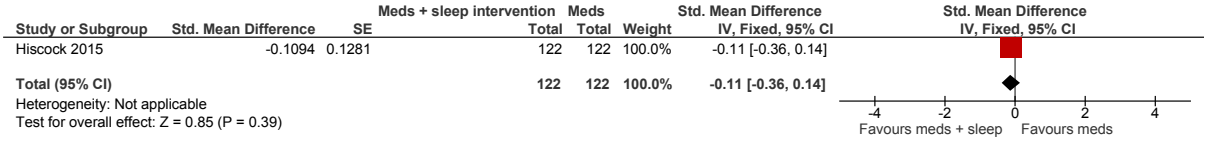


Figure 189: ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months)

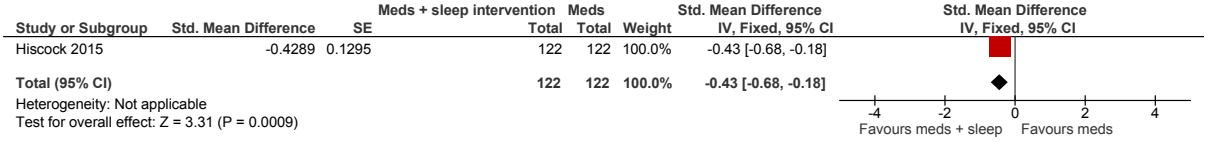


Figure 190: ADHD symptoms (inattention, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

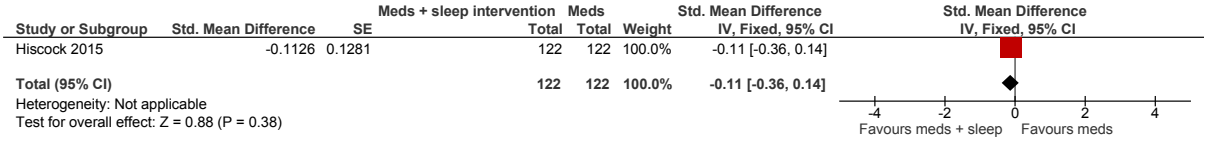


Figure 191: ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months)

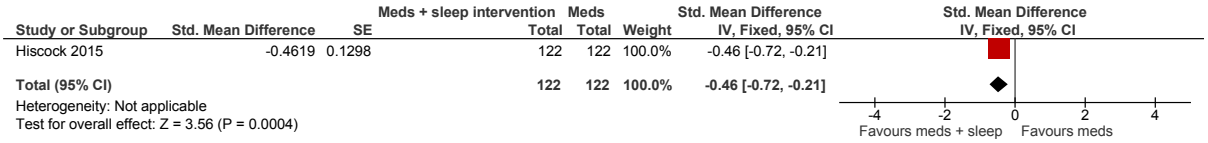


Figure 192: Behaviour/function (teacher, SDQ, 0-54, high is poor, CS, <3 months PT

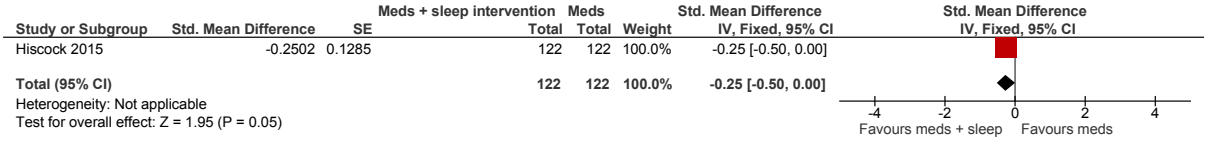
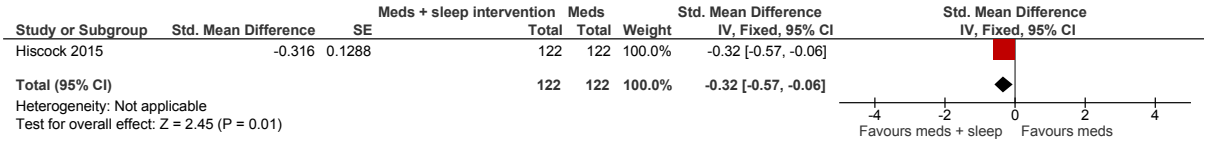


Figure 193: Behaviour/function (teacher, SDQ, 0-54, high is poor, CS, >3 months PT



E.1.3.10 Mixed medication + NF versus mixed medication

Figure 194: ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, FV, PT <3 months)

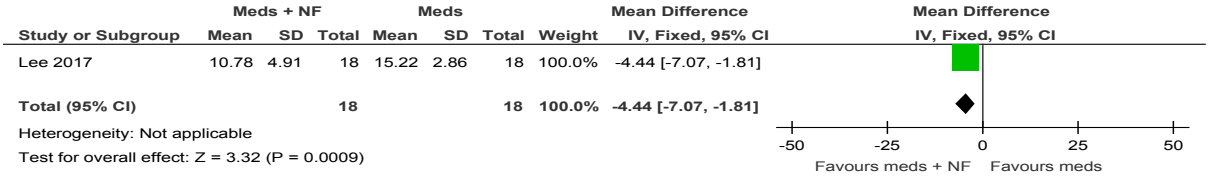
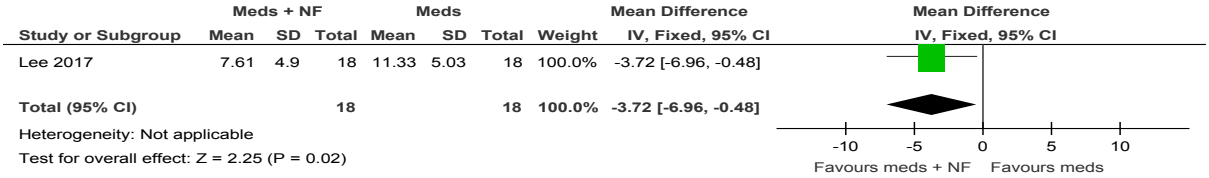


Figure 195: Behaviour/function (CBRS, parent, unclear scale, high is poor, FV, PT <3 months)



E.1.4 Combined treatment versus no treatment/usual care

E.1.4.1 Atomoxetine + PT/FT versus placebo

Figure 196: ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

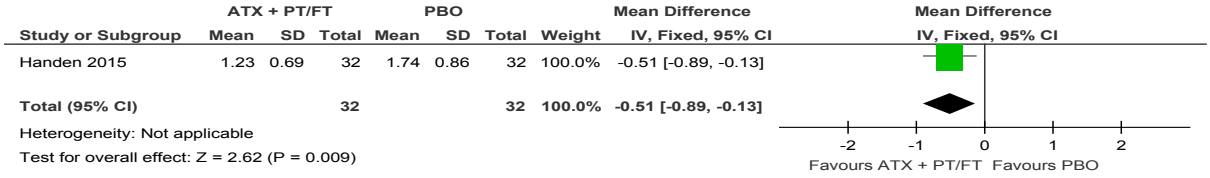


Figure 197: ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

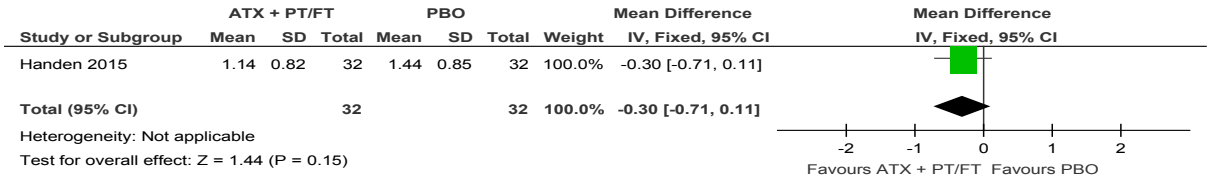


Figure 198: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

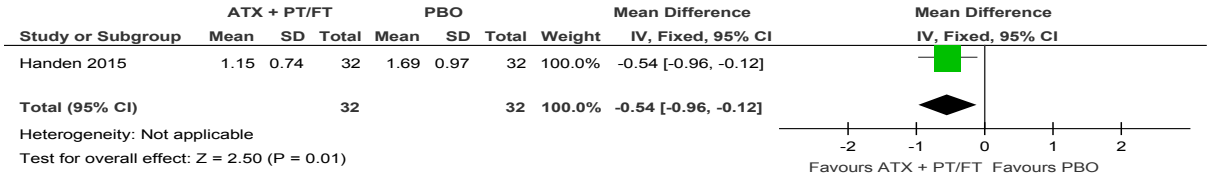


Figure 199: ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

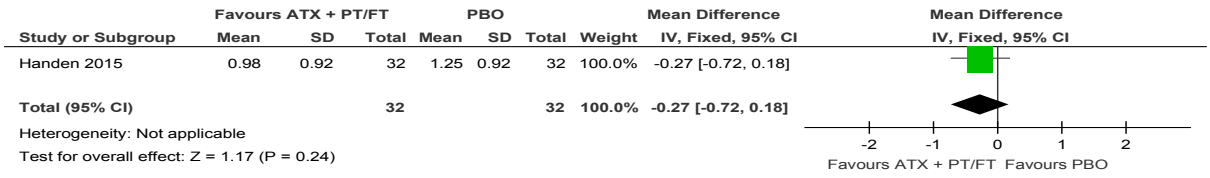


Figure 200: ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months)

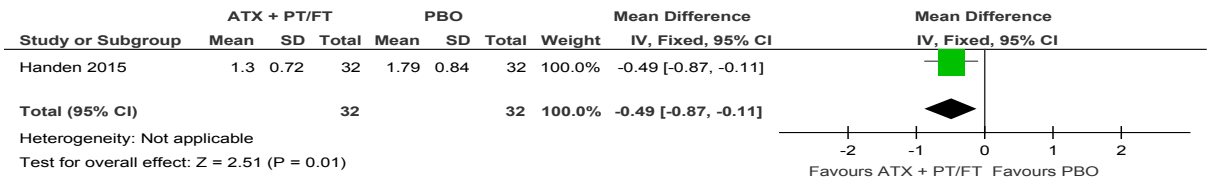


Figure 201: ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months)

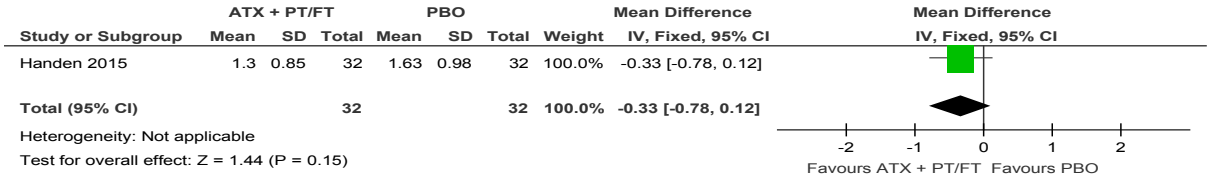
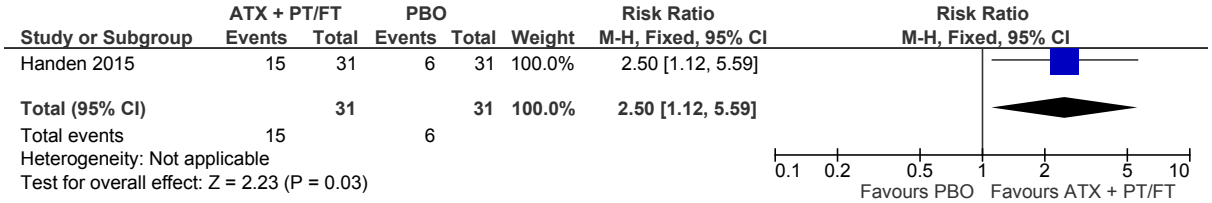


Figure 202: Responders by CGI-I (PT, <3 months)



E.1.4.2 Mixed medication + PT/FT versus usual care

Figure 203: ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months)

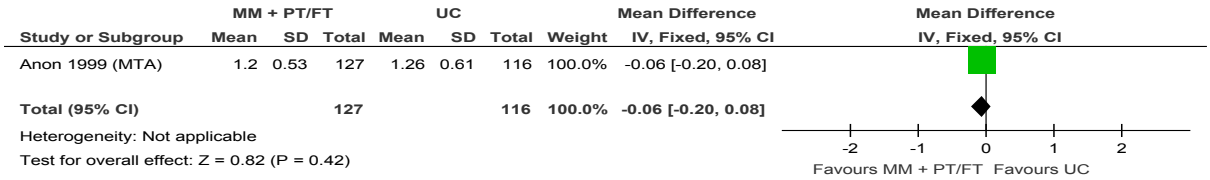


Figure 204: ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months)

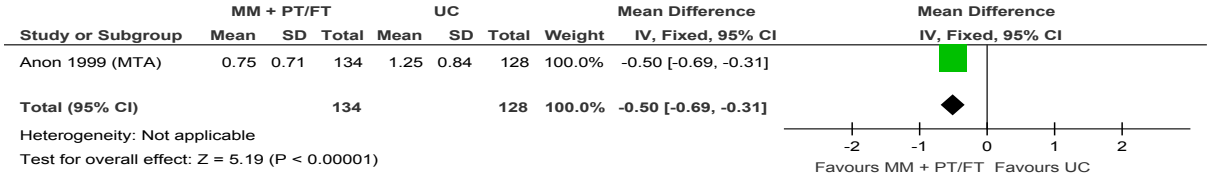


Figure 205: ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

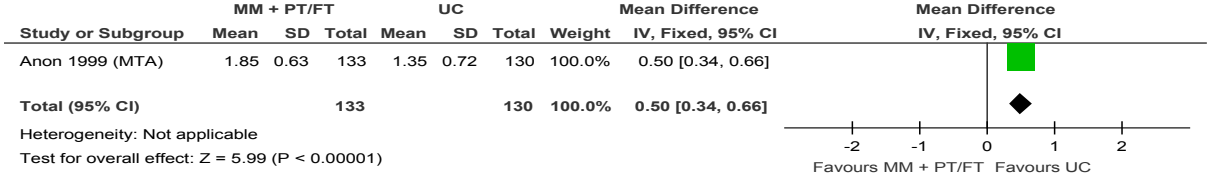


Figure 206: ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months)

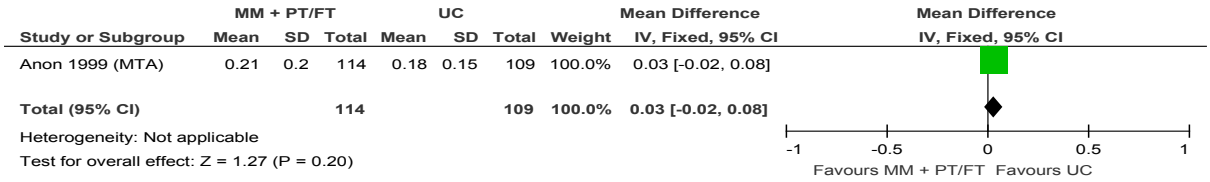


Figure 207: ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months)

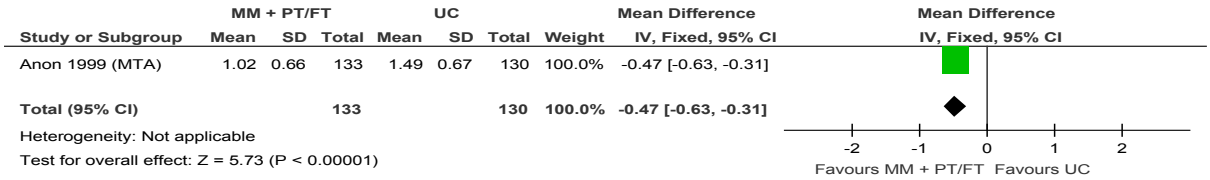


Figure 208: ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months)

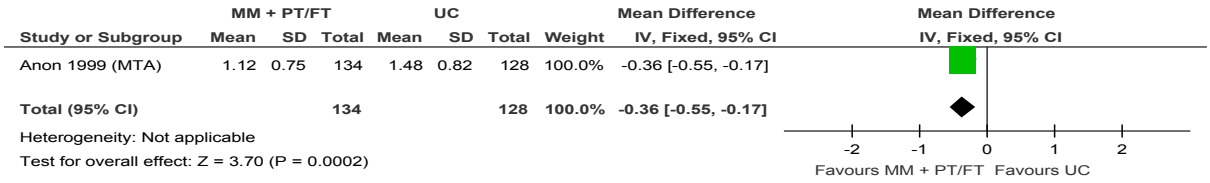


Figure 209: Academic outcomes (maths accuracy %, observer, high is better, PT <3 months)

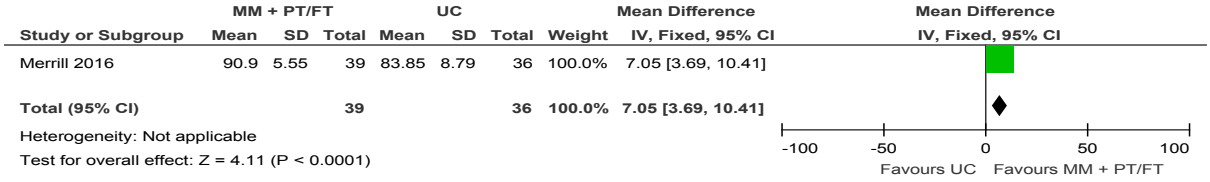


Figure 210: Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

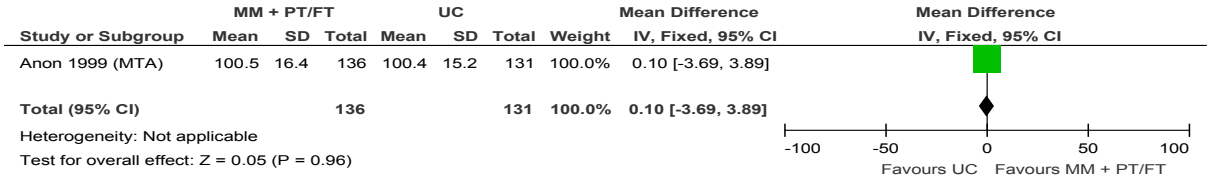


Figure 211: Academic outcomes (reading accuracy %, observer, high is better, PT <3 months)

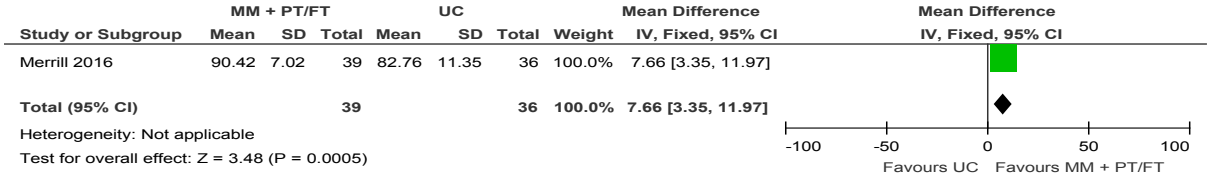


Figure 212: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months)

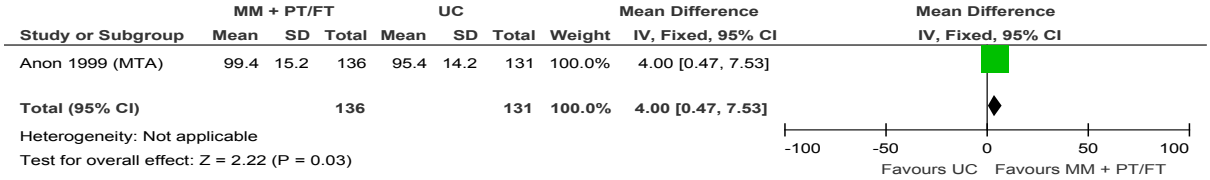
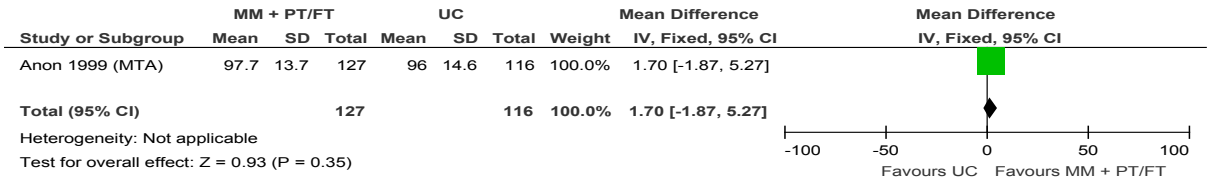


Figure 213: Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months)



E.1.5 Combined treatment versus other combined treatment

E.1.5.1 Stimulants + NF versus stimulants + attention/memory/cognitive training

Figure 214: ADHD symptoms (total, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months)

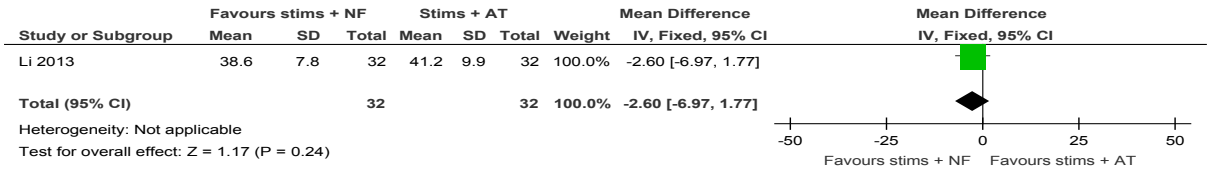


Figure 215: ADHD symptoms (total, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months)

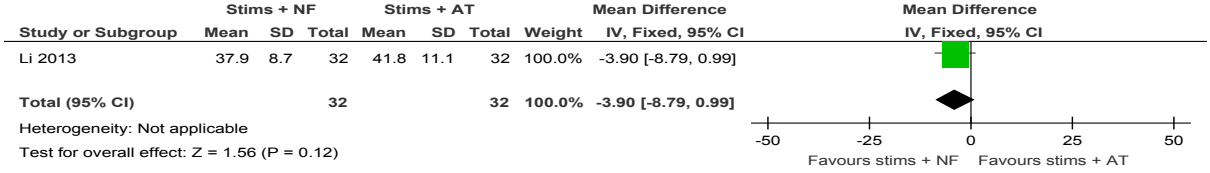


Figure 216: ADHD symptoms (total, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months)

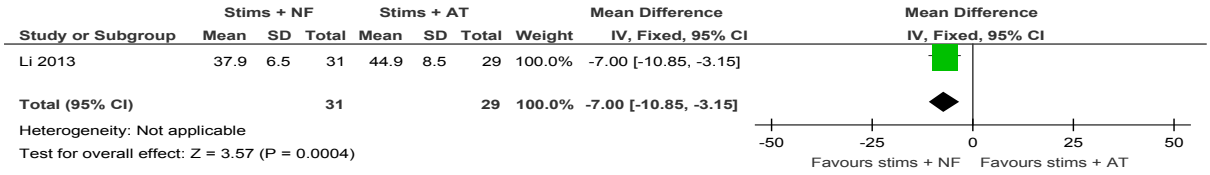


Figure 217: ADHD symptoms (total, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months)

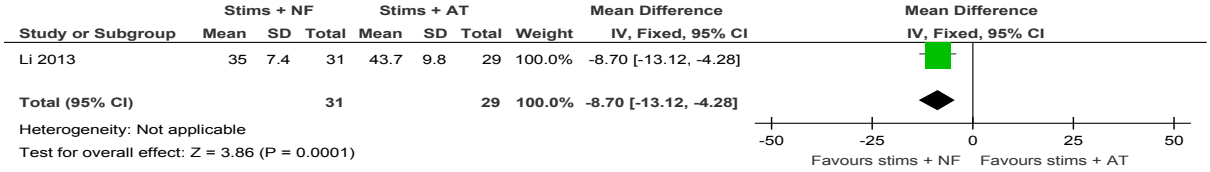


Figure 218: ADHD symptoms (hyperactivity, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months)

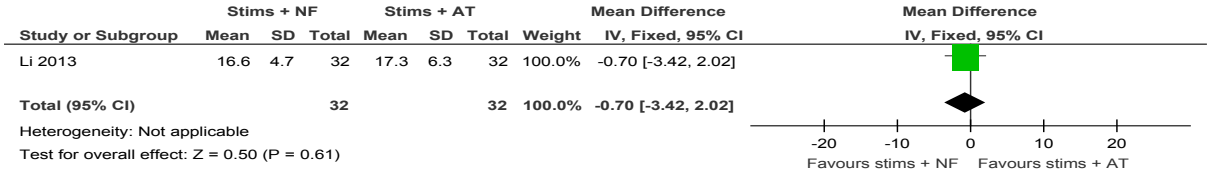


Figure 219: ADHD symptoms (hyperactivity, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months)

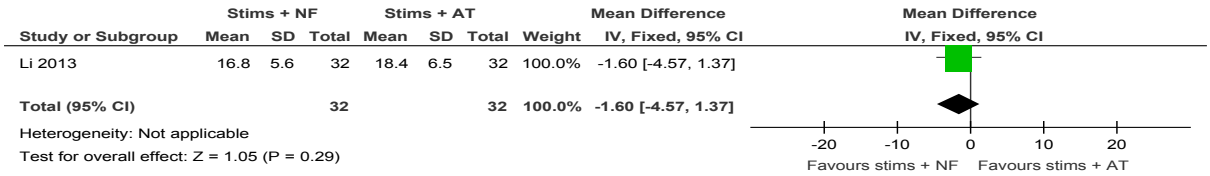


Figure 220: ADHD symptoms (hyperactivity, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months)

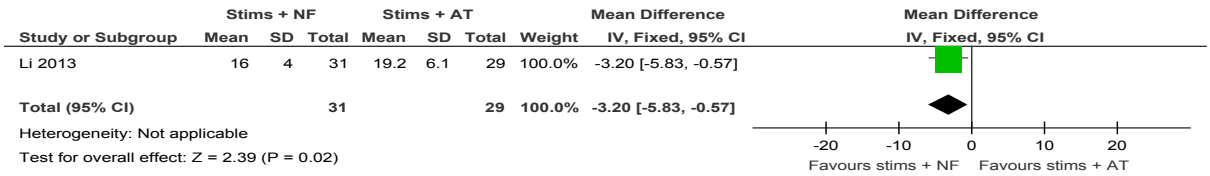


Figure 221: ADHD symptoms (hyperactivity, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months)

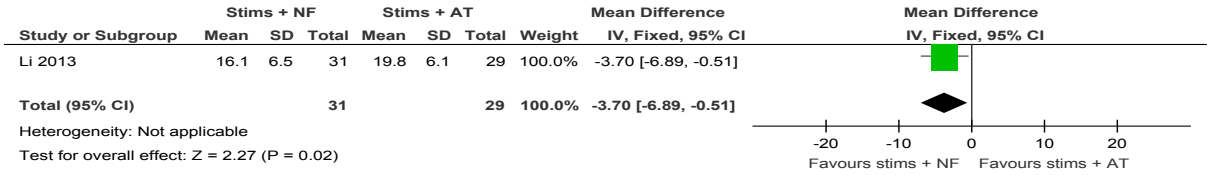


Figure 222: ADHD symptoms (inattention, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months)

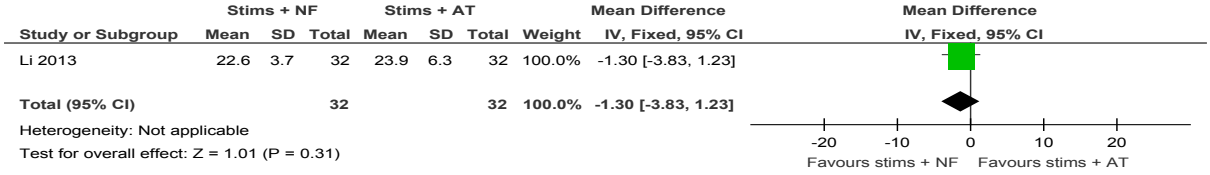


Figure 223: ADHD symptoms (inattention, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months)

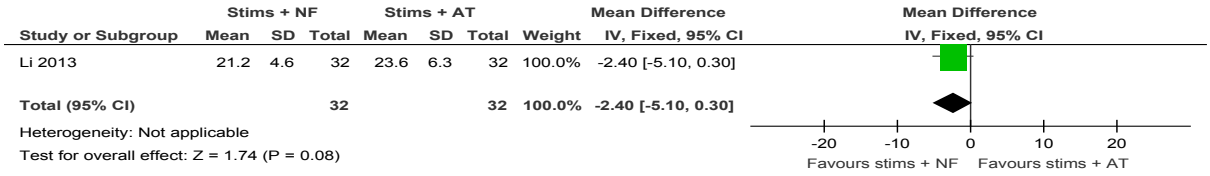


Figure 224: ADHD symptoms (inattention, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months)

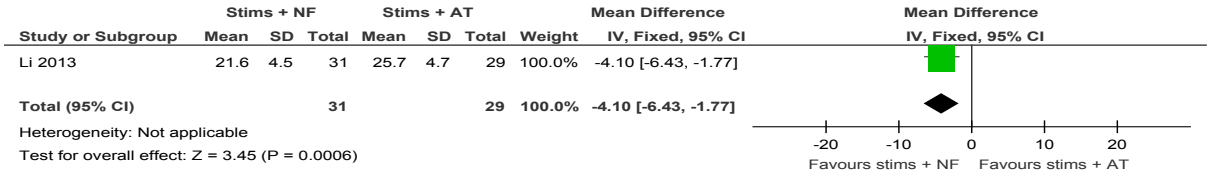
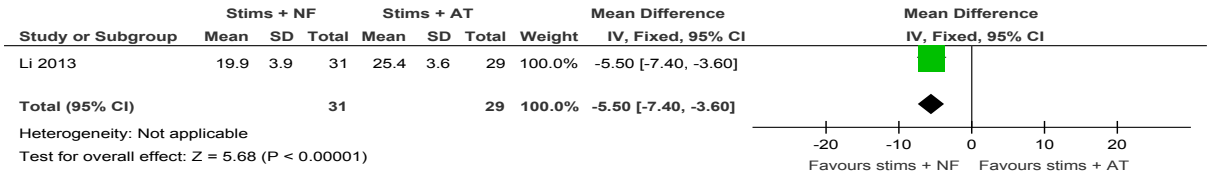


Figure 225: ADHD symptoms (inattention, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months)



E.2 Adults over the age of 18

E.2.1 Pharmacological treatment versus non-pharmacological treatment

E.2.1.1 Stimulants + NSST versus CBT alone

Figure 226: ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)

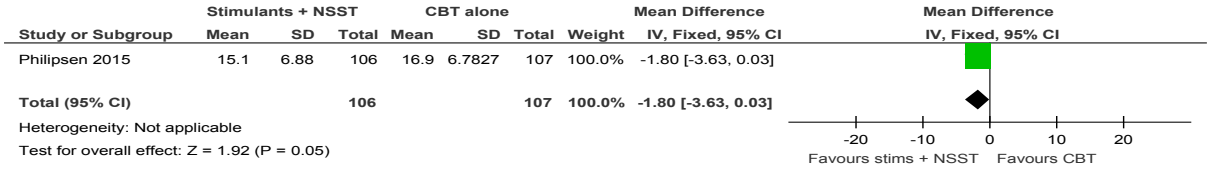


Figure 227: ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

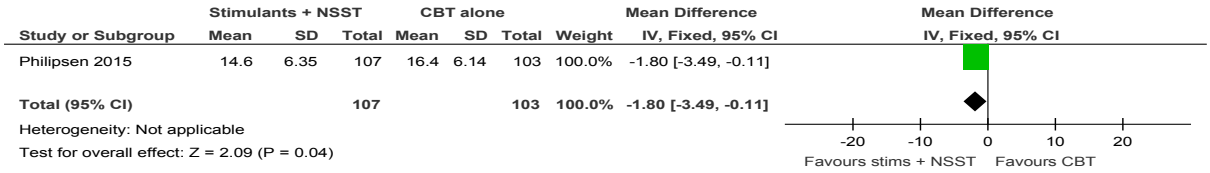


Figure 228: ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

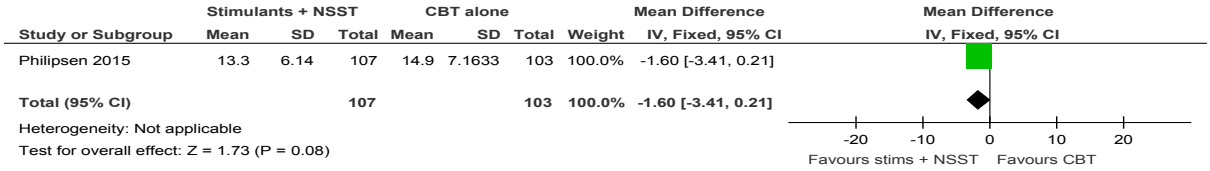


Figure 229: ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

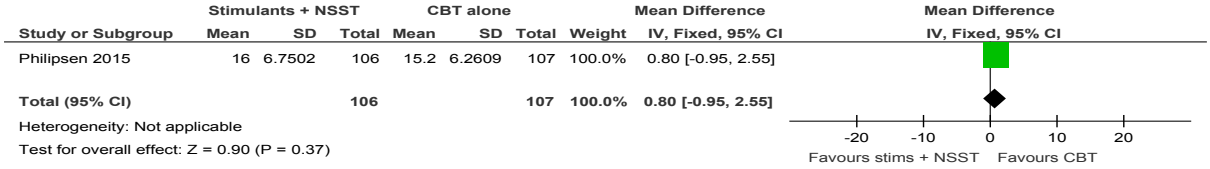
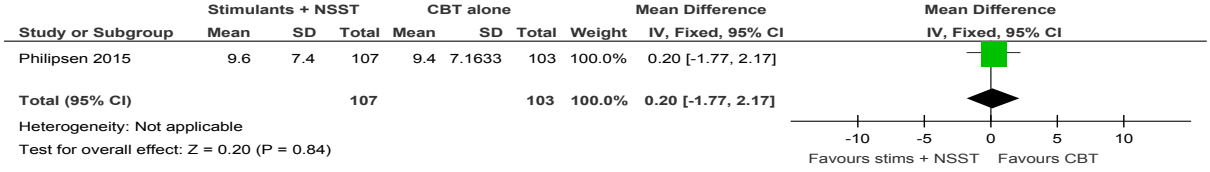


Figure 230: Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT)



E.2.2 Combined treatment versus non-pharmacological treatment

E.2.2.1 Stimulants + CBT/DBT versus CBT/DBT alone

Figure 231: ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)

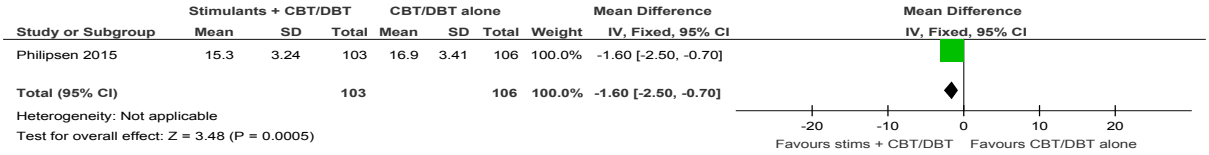


Figure 232: ADHD symptoms (total, self, multiple tools, decreased by >30%, >3 months PT)

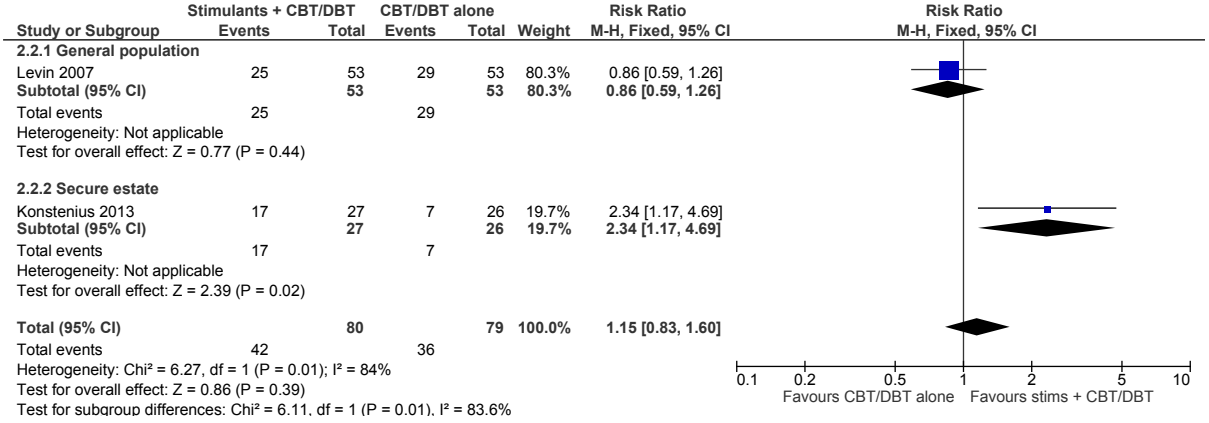


Figure 233: ADHD symptoms (total, observer, TAADDS, decreased by >30%, >3 months PT)

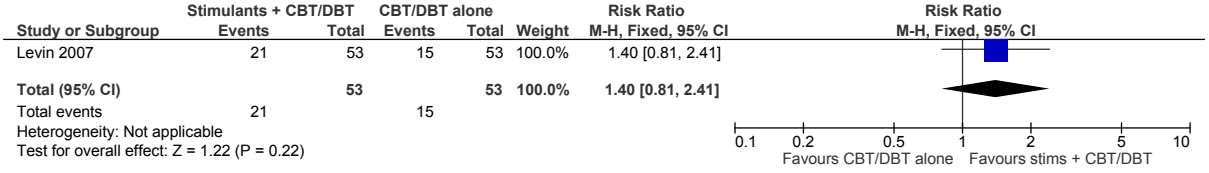


Figure 234: ADHD symptoms (total, observer, multiple tools, high is worse, FV, >3 months PT)

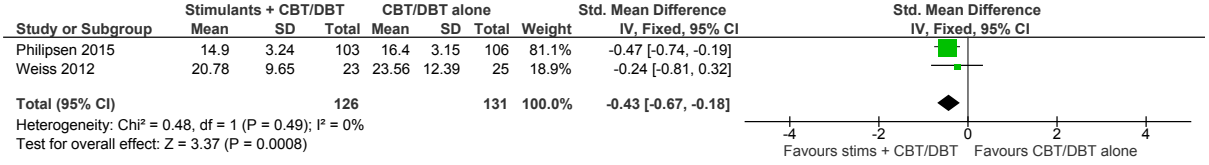


Figure 235: ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

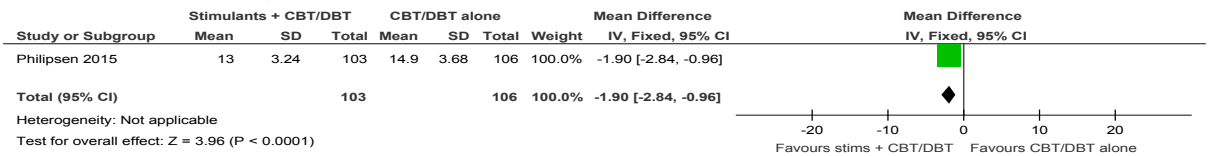


Figure 236: ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

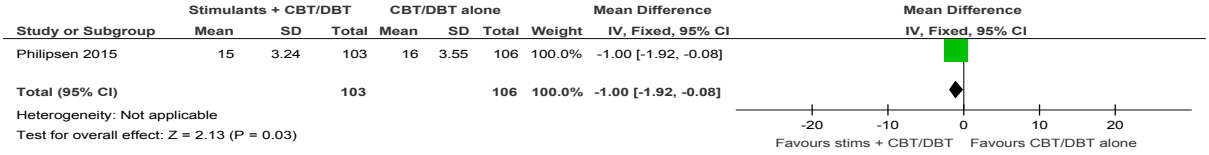


Figure 237: Emotional dysregulation (multiple tools, 0-15, high is poor, FV, >3 months PT)

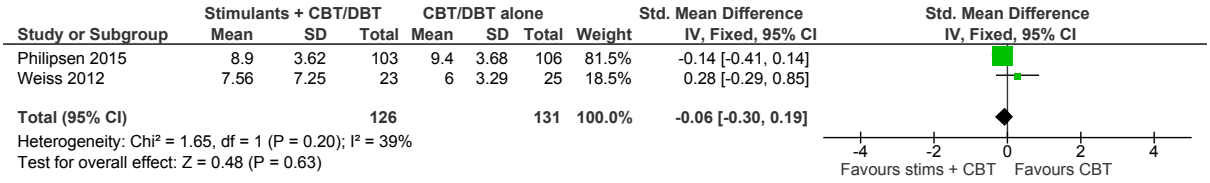


Figure 238: Responders by CGI-I (>3 months PT)

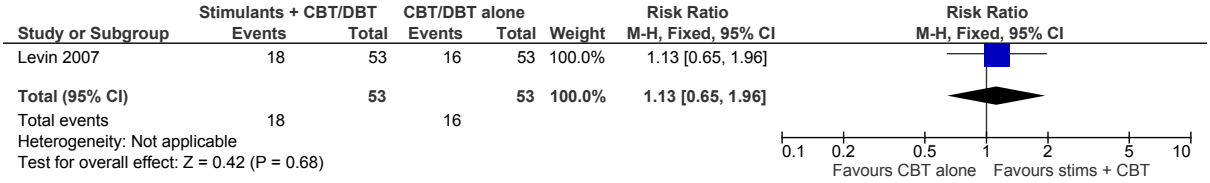
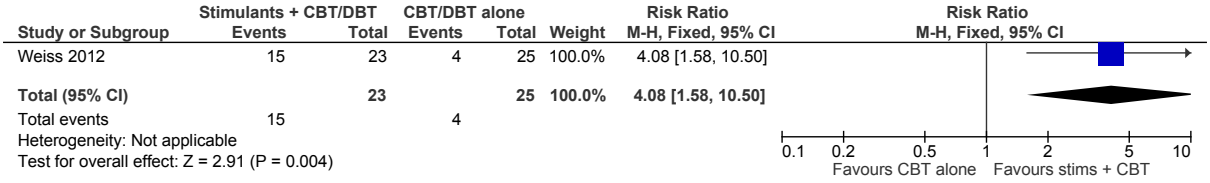


Figure 239: Responders by CGI-I (>3 months FU)



E.2.2.2 Stimulants + CBT/DBT + PT/FT versus NSST + PT/FT

Figure 240: ADHD symptoms (total, observer, CAARS, 0-36, high is poor, FV, >3 months PT)

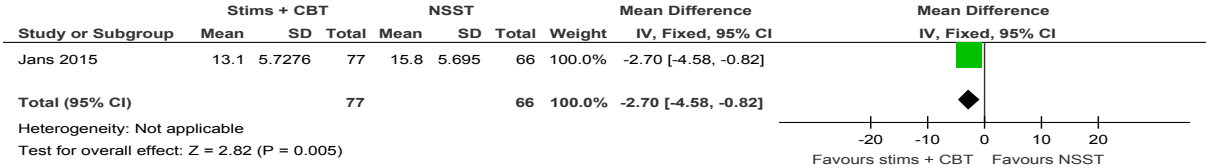


Figure 241: ADHD symptoms (hyperactivity, observer, CAARS, 0-36, high is poor, FV, >3 months PT)

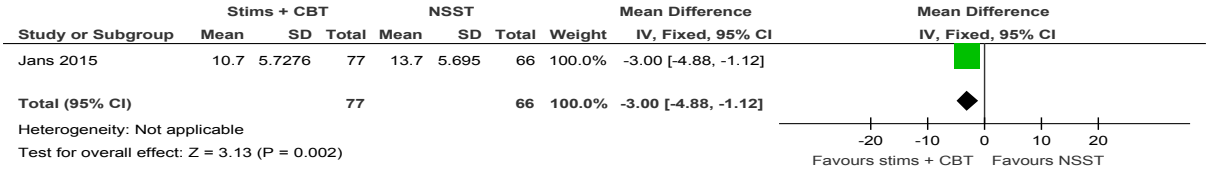


Figure 242: ADHD symptoms (inattention, observer, CAARS, 0-36, high is poor, FV, >3 months PT)

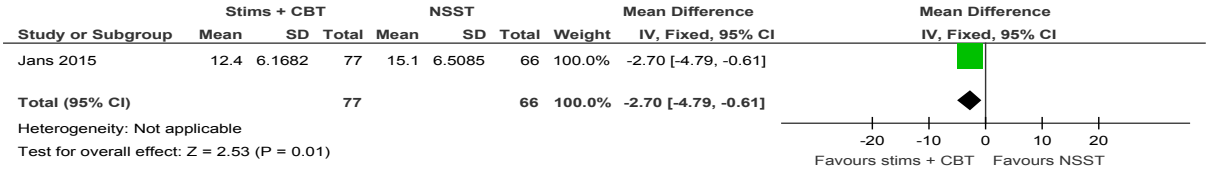


Figure 243: Child's ADHD symptoms (total, parent, SDQ, 0-10, high is poor, FV, >3 months PT)

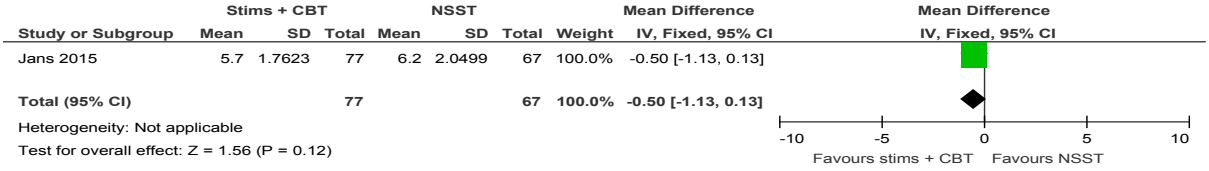
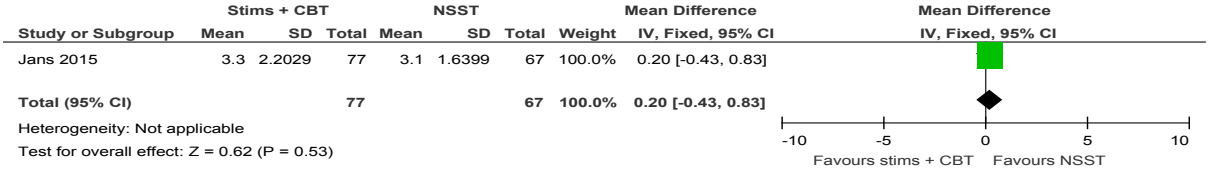


Figure 244: Emotional dysregulation (parent, SDQ, 0-10, high is poor, FV, >3 months PT)



E.2.3 Combined treatment versus pharmacological treatment

E.2.3.1 Stimulants + CBT/DBT versus stimulants + NSST

Figure 245: ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)

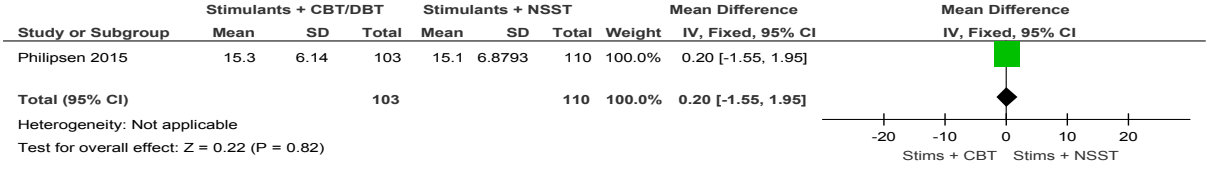


Figure 246: ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

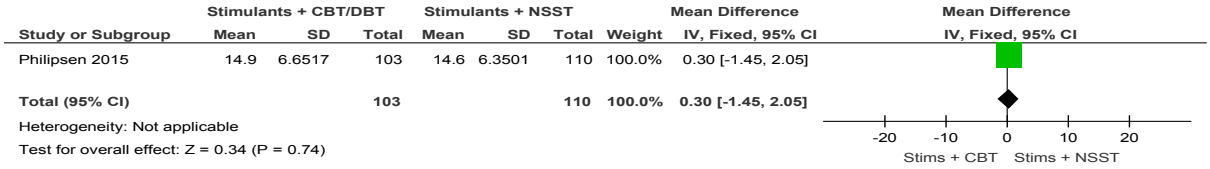


Figure 247: ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

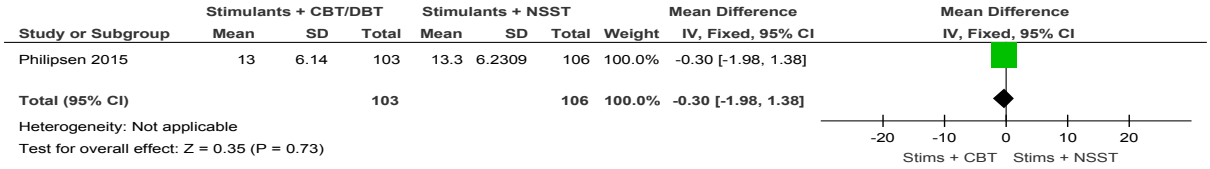


Figure 248: ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

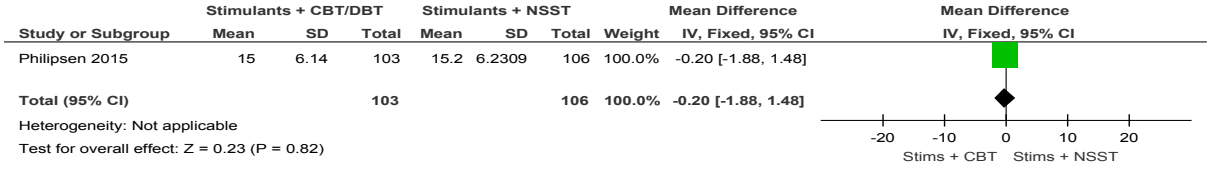
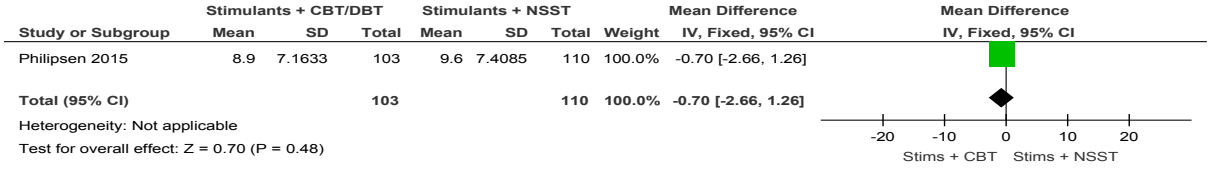


Figure 249: Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT)



E.2.3.2 Mixed medication + CBT/DBT versus mixed medication alone

Figure 250: QoL (Flanagan, 16-112, high is good, FV, <3 months PT)

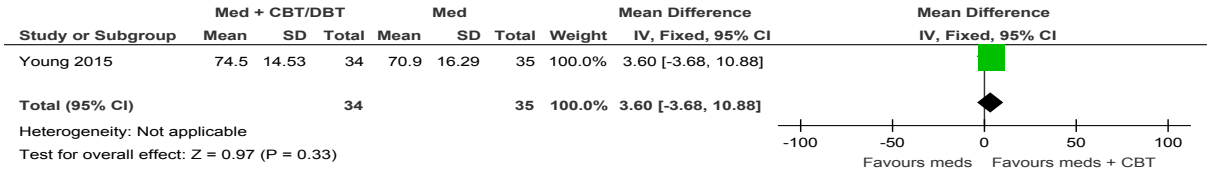


Figure 251: QoL (Flanagan, 16-112, high is good, FV, <3 months FU)

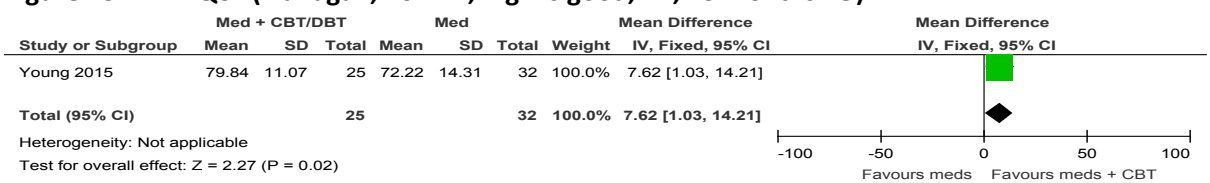


Figure 252: ADHD symptoms (total, observer, ADHD-RS, 0-54, higher is worse, FV, PT >3 months)

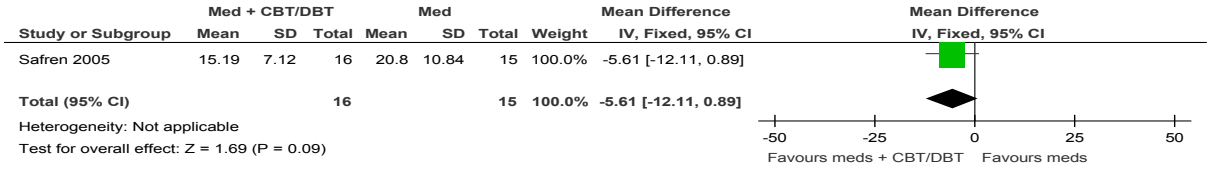


Figure 253: ADHD symptoms (total, self, ADHD-RS, 0-54, higher is worse, FV, PT >3 months)

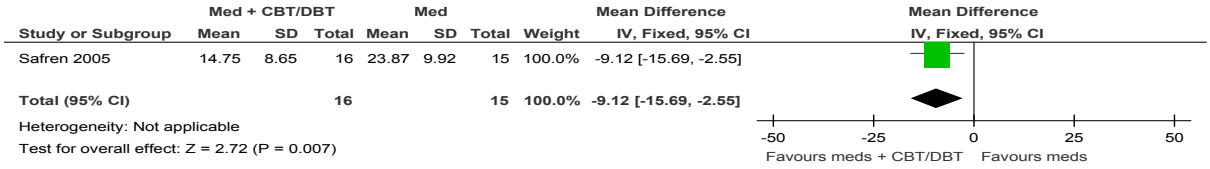


Figure 254: ADHD symptoms (total, self, Barkley, 0-54, high is poor, FV, <3 months PT)

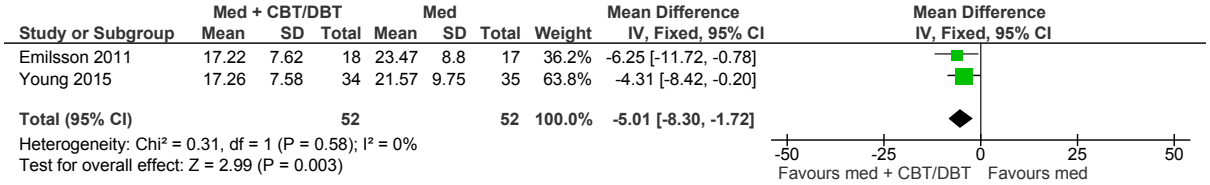


Figure 255: ADHD symptoms (total, self, Barkley, 0-54, high is poor, FV, <3 months FU)

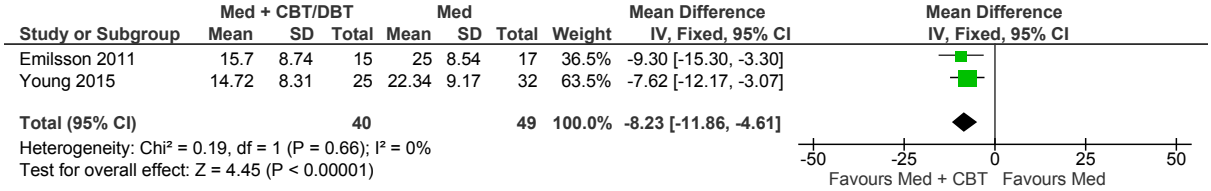


Figure 256: ADHD symptoms (hyperactivity, self, Barkley, 0-27, high is poor, FV, <3 months PT)

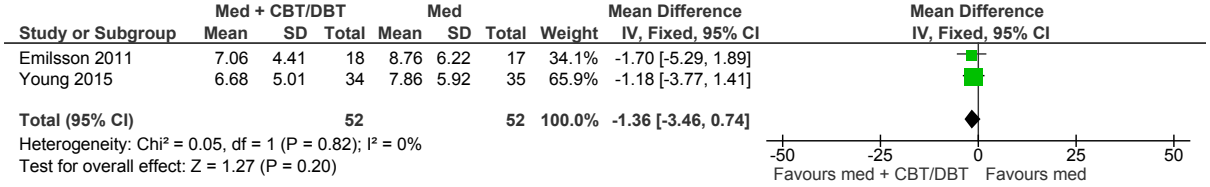


Figure 257: ADHD symptoms (hyperactivity, self, Barkley, 0-27, high is poor, FV, <3 months FU)

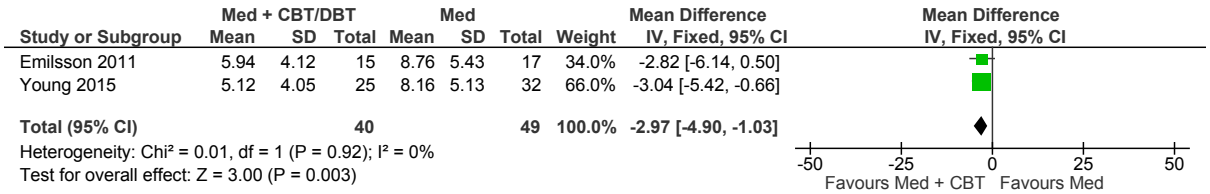


Figure 258: ADHD symptoms (inattention, self, Barkley, 0-27, high is poor, FV, <3 months PT)

Study or Subgroup	Med + CBT/DBT Mean	SD	Total	Med Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Emilsson 2011	10.17	4.44	18	14.71	5.19	17	36.0%	-4.54 [-7.75, -1.33]
Young 2015	10.59	4.4	34	13.71	5.72	35	64.0%	-3.12 [-5.52, -0.72]
Total (95% CI)			**52**			**52**	**100.0%**	**-3.63 [-5.55, -1.71]**

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 3.70 (P = 0.0002)

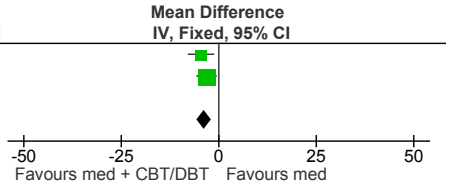


Figure 259: ADHD symptoms (inattention, self, Barkley, 0-27, high is poor, FV, <3 months FU)

Study or Subgroup	Med + CBT/DBT Mean	SD	Total	Med Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Emilsson 2011	9.76	5.62	15	16.24	5.66	17	35.6%	-6.48 [-10.40, -2.56]
Young 2015	9.6	5.34	25	14.19	5.85	32	64.4%	-4.59 [-7.50, -1.68]
Total (95% CI)			**40**			**49**	**100.0%**	**-5.26 [-7.60, -2.93]**

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.41 (P < 0.0001)

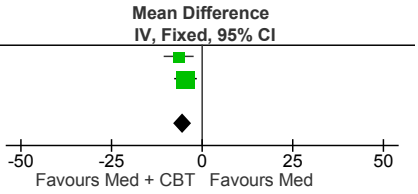


Figure 260: Responders by CGI

Study or Subgroup	Med + CBT/DBT Events	Total	Med Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Safren 2005	9	16	2	15	100.0%	4.22 [1.08, 16.45]
Total (95% CI)		**16**		**15**	**100.0%**	**4.22 [1.08, 16.45]**
Total events	9		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.07 (P = 0.04)

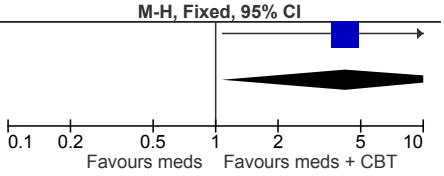


Figure 261: Emotional dysregulation (HAM-D, observer, 0-53, high is worse, FV, >3 months PT)

Study or Subgroup	Med + CBT/DBT Mean	SD	Total	Med Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Safren 2005	4.44	2.7	16	10	7.78	15	100.0%	-5.56 [-9.71, -1.41]
Total (95% CI)			**16**			**15**	**100.0%**	**-5.56 [-9.71, -1.41]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.62 (P = 0.009)

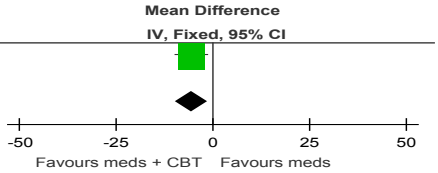


Figure 262: Emotional dysregulation (Self, BDI, 0-64, high is worse, FV, <3 months PT)

Study or Subgroup	Med + CBT/DBT Mean	SD	Total	Med Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Young 2015	8.38	6.99	34	14	10.45	34	100.0%	-5.62 [-9.85, -1.39]
Total (95% CI)			**34**			**34**	**100.0%**	**-5.62 [-9.85, -1.39]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)

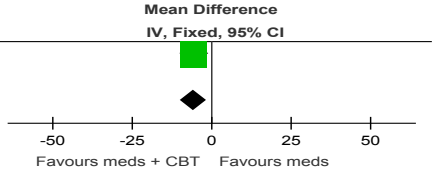


Figure 263: Emotional dysregulation (Self, BDI, 0-64, high is worse, FV, <3 months FU)

Study or Subgroup	Med + CBT/DBT Mean	SD	Total	Med Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Young 2015	5.04	5.6	24	13.14	7.99	29	100.0%	-8.10 [-11.77, -4.43]
Total (95% CI)			**24**			**29**	**100.0%**	**-8.10 [-11.77, -4.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.32 (P < 0.0001)

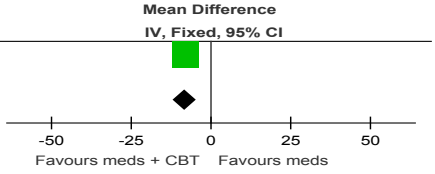


Figure 264: Behaviour/function (Self-rated, RATE antisocial scale, unclear range, high is worse, FV, <3 months PT)

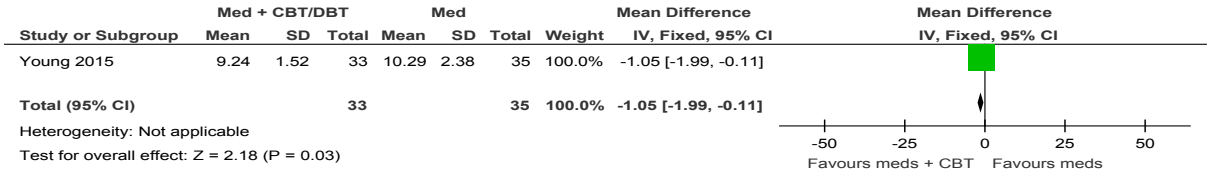
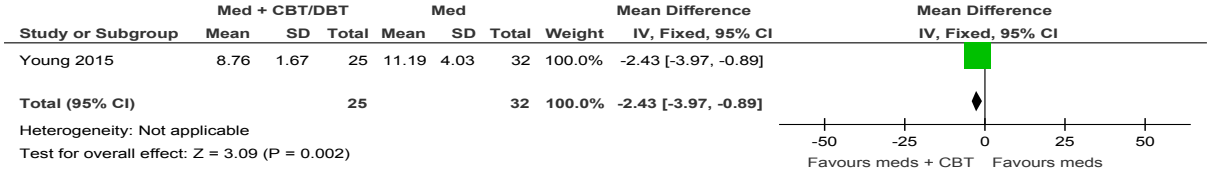


Figure 265: Behaviour/function (Self-rated, RATE antisocial scale, unclear range, high is worse, FV, <3 months FU)



E.2.3.3 Mixed medication + CBT/DBT versus mixed medication + NSST

Figure 266: QoL (QLESQ, unclear scale, high is better, FV, >3 months PT)

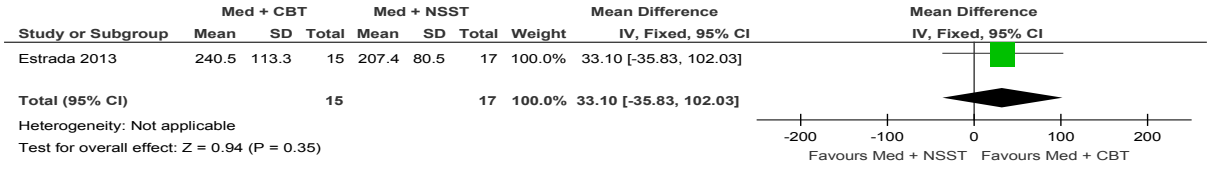


Figure 267: ADHD symptoms (total, self, ADHD-RS, high is worse, FV, 0-54, >3 months PT)

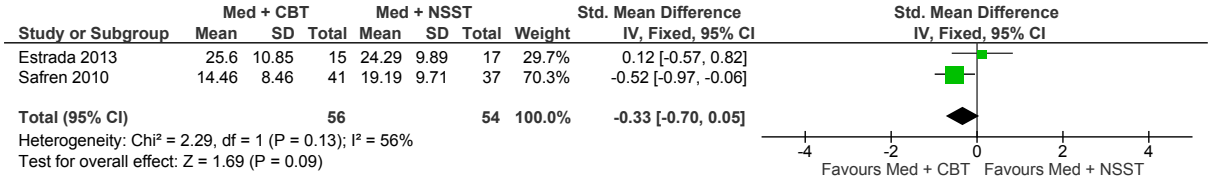


Figure 268: ADHD symptoms (total, self, ADHD-RS, high is worse, FV, 0-54, >3 months FU)

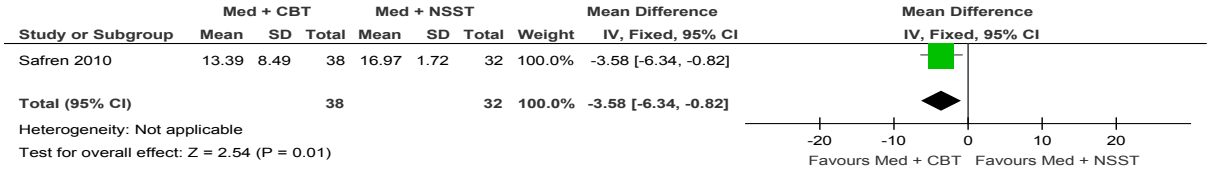


Figure 269: ADHD symptoms (hyperactivity, self, CAARS, high is worse, FV, 0-27, >3 months PT)

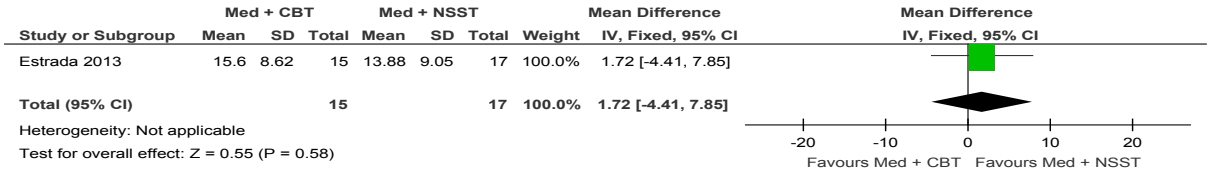


Figure 270: ADHD symptoms (inattention, self, CAARS, high is worse, FV, 0-27, >3 months PT)

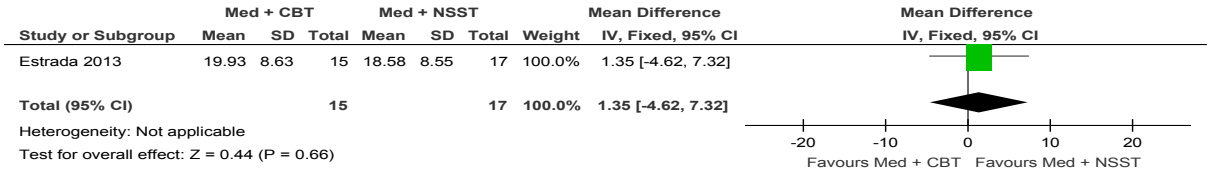


Figure 271: CGI-I responders (>3 months PT)

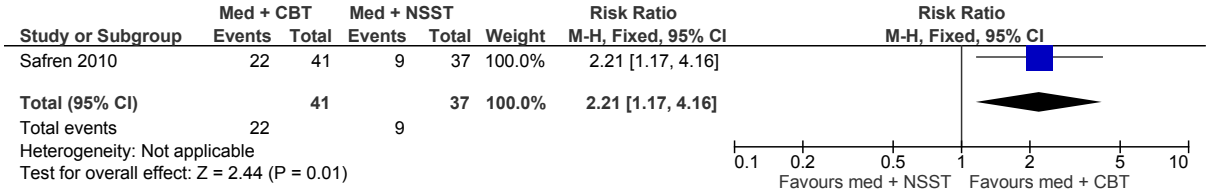
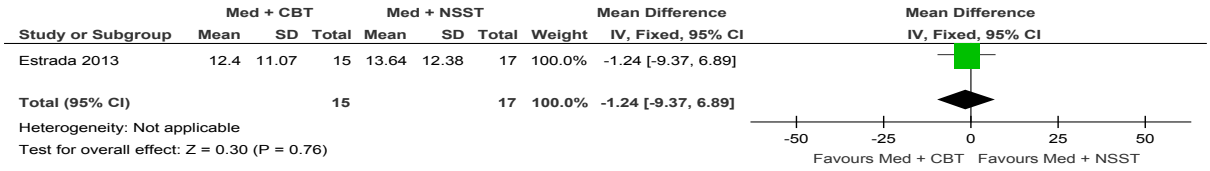


Figure 272: Emotional dysregulation (Self, BDI, 0-63, high is worse, FV, >3 months PT)



E.2.4 Combined treatment versus no treatment/usual care

E.2.4.1 Stimulants + CBT/DBT versus NSST alone

Figure 273: ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT)

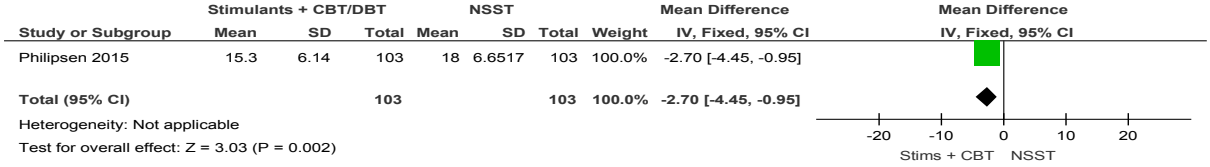


Figure 274: ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

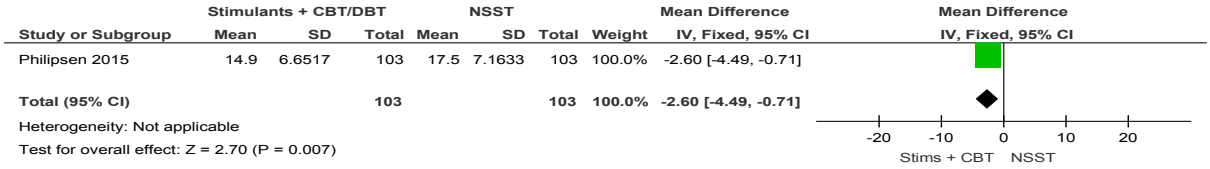


Figure 275: ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

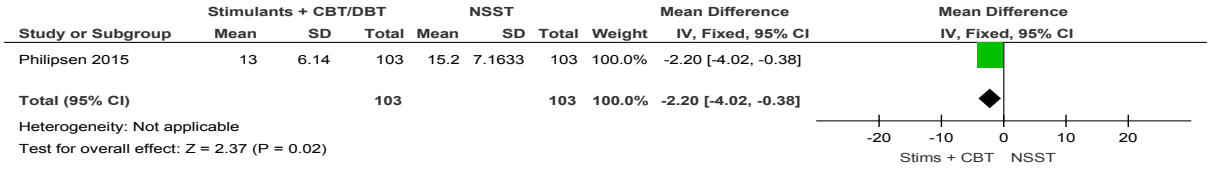


Figure 276: ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT)

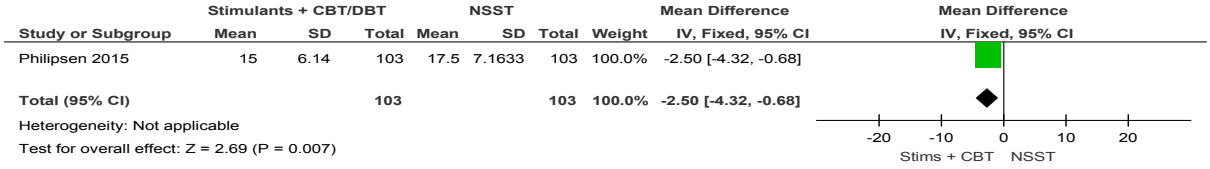
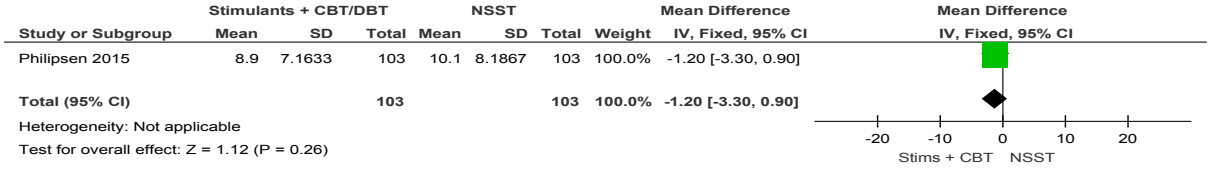


Figure 277: Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT)



Appendix F: GRADE tables

Children and young people (5-18 years old)

DRUGS versus NON-DRUGS

Table 49: Clinical evidence profile: Atomoxetine versus Parent/Family training for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine	PT/FT	Relative (95% CI)	Absolute		
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.21 lower (0.5 lower to 0.08 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.03 higher (0.35 lower to 0.41 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.32 lower (0.68 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.04 higher (0.43 lower to 0.51 higher)	⊕OOO VERY LOW	CRITICAL

ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.09 lower (0.41 lower to 0.23 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.02 higher (0.37 lower to 0.41 higher)	⊕OOO VERY LOW	CRITICAL
Responders by CGI-I (PT, <3 months) (follow-up 10 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/32 (46.9%)	29%	RR 1.61 (0.83 to 3.13)	177 more per 1000 (from 49 fewer to 618 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 50: Clinical evidence profile: Stimulants versus exercise for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants**	**Exercise**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (hyperactivity, parent, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	37	-	MD 0.45 lower (0.84 to 0.06 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	37	-	MD 0.87 lower (1.3 to 0.44 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	37	-	MD 0.50 lower (0.86 to 0.14 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, teacher, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	37	-	MD 0.76 lower (1.12 to 0.4 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 51: Clinical evidence profile: Stimulants versus Neurofeedback for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants**	**NF**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 4.60 higher (0.46 to 8.74 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	28	24	-	MD 0.30 lower (5.21 lower to 4.61 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 2.70 higher (2.93 lower to 8.33 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised	very	no serious	no serious	serious[2]	none	28	24	-	MD 0.80 higher (4.45 lower to	⊕OOO	CRITICAL

	trials	serious[1]	inconsistency	indirectness						6.05 higher)	VERY LOW	
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 3.00 higher (0.49 to 5.51 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 1.40 higher (1.43 lower to 4.23 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	36	39	-	MD 0.40 lower (0.79 to 0.01 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 0.40 higher (3.33 lower to 4.13 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 2.50 higher (0.59 lower to 5.59 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	33	39	-	MD 0.93 lower (1.39 to 0.47 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	27	25	-	MD 0.10 lower (1.63 lower to 1.43 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 0.60 higher (0.90 lower to 2.10 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 0.10 higher (1.18 lower to 1.38 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 1.60 higher (0.91 lower to 4.11 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 1.80 lower (4.42 lower to 0.82 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	36	39	-	MD 0.50 lower (0.84 to 0.16 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 2.30 higher (0.55 lower to 5.15 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 1.70 lower (4.53 lower to 1.13 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, SWAN, 0-3, high is poor, FV, PT <3 months) (follow-up 10-12 weeks; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	33	39	-	MD 0.73 lower (1.09 to 0.37 lower)	⊕⊕OO LOW	CRITICAL

ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 0.20 higher (1.02 lower to 1.42 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 0.40 higher (0.68 lower to 1.48 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	25	-	MD 0.40 lower (1.75 lower to 0.95 higher)	⊕OOO VERY LOW	CRITICAL
Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	24	-	MD 1.40 lower (3.22 lower to 0.42 higher)	⊕OOO VERY LOW	IMPORTANT
Academic (general, self, SRQ, 1-10, high is good, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	30	-	MD 0.60 higher (0.90 lower to 2.10 higher)	⊕OOO VERY LOW	IMPORTANT
Academic (general, self, SRQ, 1-10, high is good, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	24	-	MD 0.10 higher (1.18 lower to 1.38 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[4] Downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 52: Clinical evidence profile: Stimulants + NSST versus stimulants for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stimulants + NSST versus stimulants	Control	Relative (95% CI)	Absolute		
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, PT >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	4	-	MD 0.10 lower (0.38 lower to 0.18 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 0.20 lower (0.44 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 0.30 lower (0.68 lower to 0.08 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	35	34	-	MD 0.40 lower (0.7 to 0.1 lower)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 53: Clinical evidence profile: Mixed medication versus PT/FT for ADHD in children and young people

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed medication	PT/FT	Relative (95% CI)	Absolute		
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	127	-	MD 0.06 lower (0.21 lower to 0.09 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	120	119	-	MD 0.28 lower (0.47 to 0.09 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	121	129	-	MD 0.33 lower (0.5 to 0.16 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	110	107	-	MD 0.13 lower (0.19 to 0.07 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	121	129	-	MD 0.28 lower (0.45 to 0.11 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	120	120	-	MD 0.36 lower (0.56 to 0.16 lower)	⊕⊕OO LOW	CRITICAL
Academic outcomes (maths accuracy, observer, %, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	39	-	MD 4.14 lower (7.04 to 1.24 lower)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	134	-	MD 0.60 lower (3.86 lower to 2.66 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Academic outcomes (reading accuracy %, observer, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	36	-	MD 5.45 lower (9.36 to 1.54 lower)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	134	-	MD 1.70 higher (1.84 lower to 5.24 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	127	-	MD 0.50 lower (3.98 lower to 2.98 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

COMBINATION versus NON-DRUGS

Table 54: Clinical evidence profile: Atomoxetine + PT/FT versus PT/FT for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Atomoxetine + PT/FT**	**PT/FT**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.22 lower (0.54 lower to 0.1 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.32 lower (0.72 lower to 0.08 higher)	⊕⊕OO LOW	CRITICAL

ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.29 lower (0.65 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.30 lower (0.77 lower to 0.17 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.15 lower (0.5 lower to 0.2 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.34 lower (0.75 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
Responders by CGI-I (PT, <3 months) (follow-up 10 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/31 (48.4%)	29%	RR 1.67 (0.86 to 3.22)	194 more per 1000 (from 41 fewer to 644 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 55: Clinical evidence profile: Atomoxetine + PE versus PE for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Atomoxetine + PE**	**PE**	**Relative (95% CI)**	**Absolute**		
Quality of life (parent rated, total CHIP-CE, unclear range, high is good outcome, CS, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	49	50	-	MD 1.40 higher (1.93 lower to 4.73 higher)	⊕⊕⊕O MODERATE	CRITICAL

ADHD symptoms (total, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	49	50	-	MD 12.70 lower (16.86 to 8.54 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	49	50	-	MD 6.20 lower (8.42 to 3.98 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
ADHD symptoms (inattention, parent, ADHD-RS, 0-25, high is poor, CS, PT, <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	49	50	-	MD 6.50 lower (8.5 to 4.5 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Academic (parent rated, academic CHIP-CE, unclear range, high is good outcome, CS, PT <3 months) (follow-up 10 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	49	50	-	MD 4.30 higher (0.83 to 7.77 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 56: Clinical evidence profile: Atomoxetine + CBT versus CBT for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine + CBT	CBT	Relative (95% CI)	Absolute		
ADHD symptoms (total, parent, DSM-IV checklist, 0-54, high is poor, CS, PT <3 months) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	33	-	MD 5.00 higher (1.87 lower to 11.87 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, self, DSM-IV checklist, 0-54, high is poor, CS, PT <3 months) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	33	-	MD 0.83 lower (7.52 lower to 5.86 higher)	⊕⊕OO LOW	CRITICAL

Responders by CGI-I (PT, <3 months) (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/32 (53.1%)	60.6%	RR 0.88 (0.57 to 1.34)	73 fewer per 1000 (from 261 fewer to 206 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 57: Clinical evidence profile: Stimulants + NF versus NF for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + NF**	**NF**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 1.10 higher (3.03 lower to 5.23 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 1.10 lower (6.01 lower to 3.81 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 0.10 higher (5.87 lower to 6.07 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 3.20 lower (8.73 lower to 2.33 higher)	⊕OOO VERY	CRITICAL

											LOW	
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 0.30 higher (2.21 lower to 2.81 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 0.90 higher (2.00 lower to 3.80 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 2.10 lower (6.03 lower to 1.83 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	29	24	-	MD 0.00 higher (3.24 lower to 3.24 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 1.20 higher (0.36 lower to 2.76 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, >3 months) (follow-up 6 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 0.10 higher (1.18 lower to 1.38 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.40 lower (2 lower to 1.2 higher)	⊕OOO VERY LOW	CRITICAL

ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 0.80 higher (1.71 lower to 3.31 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 2.10 lower (4.79 lower to 0.59 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 2.20 higher (0.78 lower to 5.18 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 3.20 lower (6.17 to 0.23 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 0.20 lower (1.42 lower to 1.02 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	24	-	MD 1.30 higher (0.22 to 2.38 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.60 lower (1.88 lower to 0.68 higher)	⊕OOO VERY LOW	CRITICAL
Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	24	-	MD 2.50 lower (4.31 to 0.69 lower)	⊕OOO VERY LOW	IMPORTANT
Academic (general, self, SRQ, 1-10, high is good, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 1.20 higher (0.36 lower to 2.76 higher)	⊕OOO VERY LOW	IMPORTANT
Academic (general, self, SRQ,1-10, high is good, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	29	24	-	MD 0.10 higher (1.18 lower to 1.38 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 58: Clinical evidence profile: Stimulants + CBT versus CBT for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + CBT**	**CBT**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, observer, ADHD-RS, 0-68, high is poor, FV, PT, >3 months) (follow-up 16 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	151	152	-	MD 0.60 higher (1.04 lower to 2.24 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Table 59: Clinical evidence profile: Mixed medication + PT/FT versus PT/FT for ADHD in children and young people

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed medication + PT/FT	PT/FT	Relative (95% CI)	Absolute		
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	127	-	MD 0.07 lower (0.21 lower to 0.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	134	119	-	MD 0.35 lower (0.53 to 0.17 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	129	-	MD 0.61 higher (0.45 to 0.77 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	114	107	-	MD 0.08 lower (0.14 to 0.02 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	133	129	-	MD 0.38 lower (0.54 to 0.22 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	134	120	-	MD 0.35 lower (0.54 to 0.16 lower)	⊕⊕OO LOW	CRITICAL
Academic outcomes (maths accuracy %, observer, high is better, PT <3 months) (follow-up 8 days; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	39	-	MD 0.99 lower (3.42 lower to 1.44 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	134	-	MD 0.20 higher (3.4 lower to 3.8 higher)	⊕⊕OO LOW	IMPORTANT

Academic outcomes (reading accuracy %, observer, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	36	-	MD 1.17 lower (4.34 lower to 2 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	134	-	MD 3.20 higher (0.39 lower to 6.79 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	127	-	MD 0.60 lower (4.02 lower to 2.82 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

COMBINATION versus DRUGS

Table 60: Clinical evidence profile: Atomoxetine + PT/FT versus atomoxetine for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Atomoxetine + PT/FT**	**Atomoxetine**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.01 lower (0.32 lower to 0.3 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.35 lower (0.73 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL

ADHD symptoms (hyperactivity, parent, multiple scales, higher is worse, FV, PT <3 months) (follow-up 8-10 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	59	-	SMD 0.21 lower (0.57 lower to 0.15 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, multiple scales, higher is worse, FV, PT <3 months) (follow-up 8-10 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	59	-	SMD 0.16 lower (0.52 lower to 0.2 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, multiple scales, higher is worse, FV, PT <3 months) (follow-up 8-10 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	59	-	SMD 0.37 lower (0.73 to 0.01 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, multiple scales, higher is worse, FV, PT <3 months) (follow-up 8-10 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61	59	-	SMD 0.38 lower (0.74 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL
Responders by CGI-I (PT, <3 months) (follow-up 8-10 weeks)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	31/60 (51.7%)	49.4%	RR 1.05 (0.73 to 1.5)	25 more per 1000 (from 133 fewer to 247 more)	⊕OOO VERY LOW	CRITICAL
Behaviour/function (behaviour, 0-100, high is good, teacher, PT, <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	27	-	MD 5.06 higher (4.59 lower to 14.71 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 61: Clinical evidence profile: Stimulants + PT/FT versus stimulants for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stimulants + PT/FT	Stimulants	Relative (95% CI)	Absolute		
ADHD symptoms (total, parent, multiple scales, high is poor, FV, PT, >3 months) (follow-up 2-12 months; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	120	104	-	SMD 0.42 lower (0.69 to 0.15 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, parent, SWAN, 0-3, high is poor, FV, FU, >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	31	-	MD 0.13 lower (0.39 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, teacher, DBDRS, 0-54, high is poor, FV, PT, <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24	21	-	MD 2.15 higher (3.48 lower to 7.78 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, FBB-ADHS, 0-3, high is poor, FV, PT, >3 months) (follow-up 12 months; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	86	-	SMD 0.05 lower (0.35 lower to 0.25 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	34	34	-	MD 0.10 lower (0.36 lower to 0.16 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	34	34	-	MD 0.30 lower (0.7 lower to 0.1 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised	very	no serious	no serious	serious[2]	none	34	34	-	MD 0.10 lower (0.46	⊕OOO	CRITICAL

	trials	serious[3]	inconsistency	indirectness						lower to 0.26 higher)	VERY LOW	
ADHD symptoms (inattention, parent, FBB-ADHS, 0-3, high is poor, FV, PT, >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51	52	-	MD 0.29 lower (0.53 to 0.05 lower)	⊕⊕OO LOW	CRITICAL
Behaviour/function (function, parent, WFIRS-P, 0-3, high is poor, FV, PT, >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51	52	-	MD 0.10 lower (0.3 lower to 0.1 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 62: Clinical evidence profile: Stimulants + PT/FT versus stimulants + NSST for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + PT/FT versus stimulants + NSST**	**Control**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, PT >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34	35	-	MD 0.20 higher (0.08 lower to 0.48 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, CTRS, 0-3, higher is worse, FV, FU >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34	35	-	MD 0.10 higher (0.11 lower to 0.31 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, PT >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	35	-	MD 0 higher (0.36 lower to 0.36 higher)	⊕⊕OO LOW	CRITICAL

ADHD symptoms (hyperactivity, teacher, CTRS, 0-3, higher is worse, FV, FU >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34	35	-	MD 0.30 higher (0.03 to 0.57 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 63: Clinical evidence profile: Stimulants + attention/memory/cognitive training versus stimulants for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + attention/memory/cognitive training**	**Stimulants**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, Conners 48, 0-70, high is poor, FV, <3 months PT) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	25	-	MD 8.67 lower (11.5 to 5.84 lower)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 64: Clinical evidence profile: Stimulants + NF versus stimulants for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + NF**	**Stimulants**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 3.50 lower (7.57 lower to 0.57 higher)	⊕OOO VERY	CRITICAL

											LOW	
ADHD symptoms (total, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0	-	-	MD 0.80 lower (5.67 lower to 4.07 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 2.60 lower (8.51 lower to 3.31 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 4.00 lower (9.55 lower to 1.55 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 2.70 lower (5.14 to 0.26 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 0.50 lower (3.27 lower to 2.27 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 2.50 lower (6.37 lower to 1.37 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 1.50 lower (5.64 lower to 2.64 higher)	⊕OOO VERY LOW	CRITICAL

ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 0.60 higher (0.83 lower to 2.03 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self-rated, SRQ, 1-10, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	29	28	-	MD 0.00 higher (1.22 lower to 1.22 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	27	-	MD 0.30 lower (1.87 lower to 1.27 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 0.80 lower (3.05 lower to 1.45 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 0.30 lower (2.94 lower to 0 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 0.10 lower (3.16 lower to 2.96 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, Barkley's, 0-54, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 1.50 lower (4.48 lower to 1.48 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 0.40 lower (1.62 lower to 0.82 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self-rated, SRQ, 1-10, high is poor, PT, >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29	28	-	MD 0.90 higher (0.18 lower to 1.98 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	27	-	MD 0.20 lower (1.58 lower to 1.18 higher)	⊕OOO VERY LOW	CRITICAL
Academic (general, self, SRQ, 1-10, high is good, CS, PT <3 months) (follow-up <3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22	27	-	MD 1.10 lower (2.84 lower to 0.64 higher)	⊕OOO VERY LOW	IMPORTANT
Academic (general, self, SRQ, 1-10, high is good, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	31	-	MD 0.60 higher (0.83 lower to 2.03 higher)	⊕OOO VERY LOW	IMPORTANT
Academic (general, self, SRQ, 1-10, high is good, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	29	28	-	MD 0.00 higher (1.22 lower to 1.22 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 65: Clinical evidence profile: Mixed medication + PT/FT versus mixed medication for ADHD in children and young people

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mixed medication + PT/FT	Mixed medication	Relative (95% CI)	Absolute		
ADHD symptoms (total, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	144	126	-	SMD 0.27 lower (0.51 to 0.03 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	115	-	MD 0.01 lower (0.15 lower to 0.13 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, teacher, Conner's, 0-20, high is poor, FV, PT, <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	27	27	-	MD 2.22 higher (4.38 lower to 8.82 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, multiple scales, high is poor, FV, PT, >3 months) (follow-up 3-14 months; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	162	147	-	SMD 0.05 lower (0.28 lower to 0.17 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	121	-	MD 0.94 higher (0.78 to 1.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	114	110	-	MD 0.05 higher (0 to 0.1 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	144	126	-	SMD 0.22 lower (0.46 lower to 0.02 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133	121	-	MD 0.10 lower (0.27 lower to 0.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	134	120	-	MD 0.01 higher (0.18 lower to 0.2 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (inattention, parent, ADHD-RS-IV, 0-54, high is poor, CS, FU, >3 months) (follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	144	126	-	SMD 0.27 lower (0.51 to 0.03 lower)	⊕OOO VERY LOW	CRITICAL
Behaviour/function (CBRS aggressive behaviour subscale, 0-15, high is poor, teacher, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	27	26	-	MD 1.58 lower (8.11 lower to 4.95 higher)	⊕OOO VERY LOW	IMPORTANT
Behaviour/function (CBRS aggressive behaviour subscale, 0-15, high is poor, teacher, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	28	27	-	MD 2.28 lower (8.8 lower to 4.24 higher)	⊕OOO VERY LOW	IMPORTANT
Emotional dysregulation (CBRS emotional distress subscale, 0-15, high is poor, teacher, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	27	26	-	MD 4.22 higher (2.14 lower to 10.58 higher)	⊕OOO VERY LOW	IMPORTANT
Emotional dysregulation (CBRS emotional distress subscale, 0-15, high is poor, teacher, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	28	27	-	MD 2.35 higher (4.16 lower to 8.86 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (maths accuracy %, observer, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	36	-	MD 3.15 higher (0.15 to 6.15 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	124	-	MD 0.80 higher (2.78 lower to 4.38 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Academic outcomes (reading accuracy %, observer, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	36	-	MD 4.28 higher (0.3 to 8.26 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	124	-	MD 1.50 higher (2.06 lower to 5.06 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Academic outcomes (reading accuracy, observer, 0-132, high is better, FU >3 months) (follow-up median 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	115	-	MD 0.10 lower (3.53 lower to 3.33 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Academic outcomes (general, CBRS academic subscale, 0-30, high is poor, teacher, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	24	26	-	MD 2.25 higher (4.95 lower to 9.45 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (general, CBRS academic subscale, 0-30, high is poor, teacher, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	26	27	-	MD 0.48 lower (7.09 lower to 6.13 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 66: Clinical evidence profile: Mixed medication + CBT versus mixed medication for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Mixed	Mixed	Relative	Absolute		

studies		bias				considerations	medication + CBT	medication	(95% CI)			
ADHD symptoms (total, self, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	46	-	SMD 1.08 lower (1.52 to 0.64 lower)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (total, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months) (follow-up 12 sessions; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	60	-	MD 7.62 lower (7.98 to 7.26 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months) (follow-up 12 sessions; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	60	-	MD 9.39 lower (9.79 to 8.99 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 4 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	46	-	SMD 2.21 lower (2.74 to 1.69 lower)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months) (follow-up 12 sessions; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	60	-	MD 3.43 lower (3.74 to 3.12 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months) (follow-up 12 sessions; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	60	-	MD 3.84 lower (4.12 to 3.56 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, self, ADHD-RS, 0-54, high is poor, FV, PT >3 months) (follow-up 12 sessions; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	60	-	MD 4.33 lower (4.51 to 4.15 lower)	⊕⊕OO LOW	CRITICAL

ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, FV, PT >3 months) (follow-up 12 sessions; Better indicated by lower values)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	60	-	MD 5.68 lower (5.89 to 5.47 lower)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

Table 67: Clinical evidence profile: Mixed medication + PE versus mixed medication + NSST for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed medication + PE**	**Mixed medication + NSST**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (hyperactivity, parent, CPRS, 0-27, high is poor, FV, PT <3 months) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42	36	-	MD 1.71 lower (3.67 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, CPRS, 0-27, high is poor, FV, FU >3 months) (follow-up 64 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	36	-	MD 1.07 lower (3.02 lower to 0.88 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, CPRS, 0-27, high is poor, FV, PT <3 months) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42	36	-	MD 3.05 lower (4.63 to 1.47 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, CPRS, 0-27, high is poor, FV, FU >3 months) (follow-up 64 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	36	-	MD 2.15 lower (3.93 to 0.37 lower)	⊕⊕OO LOW	CRITICAL
Behaviour/function (opposition, parent, CPRS, 0-27, high is poor, FV, PT <3 months) (follow-up 12 weeks; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42	36	-	MD 1.23 lower (2.94 lower to 0.48 higher)	⊕⊕OO LOW	IMPORTANT
Behaviour/function (opposition, parent, CPRS, 0-27, high is poor, FV, FU >3 months) (follow-up 64 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	36	-	MD 0.43 lower (2.21 lower to 1.35 higher)	⊕⊕OO LOW	IMPORTANT
Emotional dysregulation (SDQ, parent, 0-25, high is poor, FV, PT <3 months) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	36	-	MD 0.11 lower (1.21 lower to 0.99 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Emotional dysregulation (SDQ, parent, 0-25, high is poor, FV, FU >3 months) (follow-up 64 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	36	-	MD 0.29 lower (1.32 lower to 0.74 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 68: Clinical evidence profile: Mixed medication + sleep intervention versus mixed medication for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed medication + sleep intervention**	**Mixed medication**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	122	-	SMD 0.21 lower (0.46 lower to 0.04 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months) (follow-up 3 months; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.39 lower (0.64 to 0.13 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	122	-	SMD 0.18 lower (0.43 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.41 lower (0.66 to 0.15 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.28 lower (0.53 to 0.03 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.27 lower (0.52 to 0.02 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 6 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	122	-	SMD 0.18 lower (0.44 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.29 lower (0.54 to 0.04 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, ADHD-RS, 0-54, high is poor, CS, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised	very	no serious	no serious	no serious	none	122	122	-	SMD 0.11 lower	⊕⊕OO	CRITICAL

	trials	serious[1]	inconsistency	indirectness	imprecision					(0.36 lower to 0.14 higher)	LOW	
ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, CS, PT <3 months) (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.43 lower (0.68 to 0.18 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	122	-	SMD 0.11 lower (0.36 lower to 0.14 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, parent, ADHD-RS, 0-54, high is poor, CS, PT >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.46 lower (0.72 to 0.21 lower)	⊕OOO VERY LOW	CRITICAL
Behaviour/function (teacher, SDQ, 0-54, high is poor, CS, <3 months PT (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	122	-	SMD 0.25 lower (0.5 lower to 0 higher)	⊕⊕OO LOW	IMPORTANT
Behaviour/function (teacher, SDQ, 0-54, high is poor, CS, >3 months PT (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	122	122	-	SMD 0.32 lower (0.57 to 0.06 lower)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 69: Clinical evidence profile: Mixed medication + NF versus mixed medication for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Mixed	Mixed	Relative	Absolute		

studies		bias				considerations	medication + NF	medication	(95% CI)			
ADHD symptoms (total, parent, ADHD-RS, 0-54, high is poor, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	18	-	MD 4.44 lower (7.07 to 1.81 lower)	⊕⊕OO LOW	CRITICAL
Behaviour/function (CBRS, parent, unclear scale, high is poor, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	18	-	MD 3.72 lower (6.96 to 0.48 lower)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

- **COMBINATION versus NOTHING**

Table 70: Clinical evidence profile: Atomoxetine + PT/FT versus placebo/usual care for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine + PT/FT	Placebo/usual care	Relative (95% CI)	Absolute		
ADHD symptoms (total, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.51 lower (0.89 to 0.13 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.30 lower (0.71 lower to 0.11 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised	very	no serious	no serious	serious[2]	none	32	32	-	MD 0.54 lower (0.96	⊕OOO	CRITICAL

	trials	serious[1]	inconsistency	indirectness						to 0.12 lower)	VERY LOW	
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.27 lower (0.72 lower to 0.18 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, parent, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.49 lower (0.87 to 0.11 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, higher is worse, FV, PT <3 months) (follow-up 10 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	-	MD 0.33 lower (0.78 lower to 0.12 higher)	⊕OOO VERY LOW	CRITICAL
Responders by CGI-I (PT, <3 months) (follow-up 10 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/31 (48.4%)	19.4%	RR 2.5 (1.12 to 5.59)	291 more per 1000 (from 23 more to 890 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.

Table 71: Clinical evidence profile: Mixed medication + PT/FT versus placebo/usual care for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mixed medication + PT/FT**	**Placebo/usual care**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, teacher and parent, SNAP, 0-3, high is poor, FV, FU >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised	serious[1]	no serious	no serious	no serious	none	127	116	-	MD 0.06 lower (0.2	⊕⊕⊕O	CRITICAL

	trials		inconsistency	indirectness	imprecision					lower to 0.08 higher)	MODERATE	
ADHD symptoms (hyperactivity, teacher, SNAP, 0-3, high is poor, FV, PT, >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	134	128	-	MD 0.50 lower (0.69 to 0.31 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	133	130	-	MD 0.50 higher (0.34 to 0.66 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, observer, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	109	-	MD 0.03 higher (0.02 lower to 0.08 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (inattention, parent, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	133	130	-	MD 0.47 lower (0.63 to 0.31 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, teacher, SNAP, 0-3, high is poor, FV, PT >3 months) (follow-up 14 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	134	128	-	MD 0.36 lower (0.55 to 0.17 lower)	⊕⊕OO LOW	CRITICAL
Academic outcomes (maths accuracy %, observer, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	36	-	MD 7.05 higher (3.69 to 10.41 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (maths accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	131	-	MD 0.10 higher (3.69 lower to 3.89 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Academic outcomes (reading accuracy %, observer, high is better, PT <3 months) (follow-up 8 weeks; Better indicated by higher values)												

1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	39	36	-	MD 7.66 higher (3.35 to 11.97 higher)	⊕OOO VERY LOW	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, PT >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	136	131	-	MD 4.00 higher (0.47 to 7.53 higher)	⊕⊕OO LOW	IMPORTANT
Academic outcomes (reading accuracy, observer, WIAT, 0-132, high is better, FU >3 months) (follow-up 14 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	116	-	MD 1.70 higher (1.87 lower to 5.27 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias.
[2] Downgraded by 1 increment if the confidence interval crossed one MID.
[3] Downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

- **COMBINATION versus OTHER COMBINATION**

Table 72: Clinical evidence profile: Stimulants + NF versus stimulants + attention/memory/cognitive training for ADHD in children and young people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + NF**	**Stimulants + attention/memory/cognitive training**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months) (follow-up 8-20 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 2.60 lower (6.97 lower to 1.77 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (total, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months) (follow-up 8-20 weeks; Better indicated by lower values)												
1	randomised	no	no serious	no serious	serious[1]	none	32	32	-	MD 3.90 lower	⊕⊕⊕O	CRITICAL

	trials	serious risk of bias	inconsistency	indirectness						(8.79 lower to 0.99 higher)	MODERATE	
ADHD symptoms (total, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	29	-	MD 7.00 lower (10.85 to 3.15 lower)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (total, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	29	-	MD 8.70 lower (13.12 to 4.28 lower)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months) (follow-up 8-20 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 0.70 lower (3.42 lower to 2.02 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months) (follow-up 8-20 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 1.60 lower (4.57 lower to 1.37 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	29	-	MD 3.20 lower (5.83 to 0.57 lower)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	29	-	MD 3.70 lower (6.89 to 0.51 lower)	⊕⊕⊕O MODERATE	CRITICAL

ADHD symptoms (inattention, parent, DSM-IV, high is poor, unclear scale, FV, PT <3 months) (follow-up 8-20 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 1.30 lower (3.83 lower to 1.23 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (inattention, teacher, DSM-IV, high is poor, unclear scale, FV, PT <3 months) (follow-up 8-20 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32	32	-	MD 2.40 lower (5.1 lower to 0.3 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (inattention, parent, DSM-IV, high is poor, unclear scale, FV, FU >3 months) (follow-up 6 weeks; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	29	-	MD 4.10 lower (6.43 to 1.77 lower)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (inattention, teacher, DSM-IV, high is poor, unclear scale, FV, FU >3 months) (follow-up 6 months; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	29	-	MD 5.50 lower (7.4 to 3.6 lower)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID.

Adults (>18 years old)

DRUGS versus NON-DRUGS

Table 73: Clinical evidence profile: Stimulants +NSST versus CBT for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of	**Design**	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stimulants +**	**Control**	**Relative**	**Absolute**		

studies		bias				considerations	NSST		(95% CI)			
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	106	107	-	MD 1.80 lower (3.63 lower to 0.03 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	107	103	-	MD 1.80 lower (3.49 to 0.11 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	107	103	-	MD 1.60 lower (3.41 lower to 0.21 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106	107	-	MD 0.80 higher (0.95 lower to 2.55 higher)	⊕⊕⊕O MODERATE	CRITICAL
Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	103	-	MD 0.20 higher (1.77 lower to 2.17 higher)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

- **COMBINATION versus NON-DRUGS**

Table 74: Clinical evidence profile: Stimulants + CBT/DBT versus CBT/DBT for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stimulants + CBT/DBT	CBT/DBT alone	Relative (95% CI)	Absolute		

ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 1 years; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	106	-	MD 1.60 lower (2.5 to 0.7 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, self, multiple tools, decreased by >30%, >3 months PT) - General population (follow-up 14 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	25/53 (47.2%)	54.7%	RR 0.86 (0.59 to 1.26)	77 fewer per 1000 (from 224 fewer to 142 more)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, self, multiple tools, decreased by >30%, >3 months PT) - Secure estate (follow-up 24 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/27 (63%)	26.9%	RR 2.34 (1.17 to 4.69)	360 more per 1000 (from 46 more to 993 more)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, observer, TAADDS, decreased by >30%, >3 months PT) (follow-up 14 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21/53 (39.6%)	28.3%	RR 1.4 (0.81 to 2.41)	113 more per 1000 (from 54 fewer to 399 more)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (total, observer, multiple tools, high is worse, FV, >3 months PT) (follow-up 20-52 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	126	131	-	SMD 0.43 lower (0.67 to 0.18 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	106	-	MD 1.90 lower (2.84 to 0.96 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	106	-	MD 1.00 lower (1.92 to 0.08 lower)	⊕⊕OO LOW	CRITICAL
Emotional dysregulation (multiple tools, high is poor, FV, >3 months PT) (follow-up 20-52 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126	131	-	SMD 0.06 lower (0.3 lower to 0.19 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Responders by CGI-I (>3 months PT) (follow-up 14 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/53 (34%)	30.2%	RR 1.12 (0.65 to 1.96)	36 more per 1000 (from 106 fewer to 290 more)	⊕⊕OO LOW	CRITICAL
Responders by CGI-I (>3 months FU) (follow-up 20 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/23 (65.2%)	16%	RR 4.08 (1.58 to 10.5)	493 more per 1000 (from 93 more to 1000 more)	⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 75: Clinical evidence profile: Stimulants + CBT/DBT + PT/FT versus NSST + PT/FT for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + CBT/DBT + PT/FT**	**NSST + PT/FT**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, observer, CAARS, 0-36, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77	66	-	MD 2.70 lower (4.58 to 0.82 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, observer, CAARS, 0-36, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77	66	-	MD 3.00 lower (4.88 to 1.12 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, observer, CAARS, 0-36, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77	66	-	MD 2.70 lower (4.79 to 0.61 lower)	⊕⊕OO LOW	CRITICAL
Child's ADHD symptoms (total, parent, SDQ, 0-10, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77	67	-	MD 0.50 lower (1.13 lower to 0.13 higher)	⊕⊕OO LOW	IMPORTANT
Emotional dysregulation (parent, SDQ, 0-10, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77	67	-	MD 0.20 higher (0.43 lower to 0.83 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

COMBINATION versus DRUGS

Table 76: Clinical evidence profile: Stimulants + CBT/DBT versus stimulants + NSST for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stimulants + CBT/DBT**	**Stimulants + NSST**	**Relative (95% CI)**	**Absolute**		
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	110	-	MD 0.20 higher (1.55 lower to 1.95 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	110	-	MD 0.30 higher (1.45 lower to 2.05 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	106	-	MD 0.30 lower (1.98 lower to 1.38 higher)	⊕⊕⊕O MODERATE	CRITICAL

ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	106	-	MD 0.20 lower (1.88 lower to 1.48 higher)	⊕⊕⊕O MODERATE	CRITICAL
Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	110	-	MD 0.70 lower (2.66 lower to 1.26 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 77: Clinical evidence profile: Medication + CBT/DBT versus medication for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Medication + CBT/DBT**	**Medication alone**	**Relative (95% CI)**	**Absolute**		
QoL (Flanagan, 16-112, high is good, FV, <3 months PT) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34	35	-	MD 3.60 higher (3.68 lower to 10.88 higher)	⊕OOO VERY LOW	CRITICAL
QoL (Flanagan, 16-112, high is good, FV, <3 months FU) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	32	-	MD 7.62 higher (1.03 to 14.21 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, observer, ADHD-RS, 0-54, higher is worse, FV, PT >3 months) (follow-up 15 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	15	-	MD 5.61 lower (12.11 lower to 0.89 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, self, ADHD-RS, 0-54, higher is worse, FV, PT >3 months) (follow-up 15 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	15	-	MD 9.12 lower (15.69 to 2.55 lower)	⊕OOO VERY	CRITICAL

											LOW	
ADHD symptoms (total, self, Barkley, 0-54, high is poor, FV, <3 months PT) (follow-up 8-12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	52	-	5.01 lower (8.30 to 1.72 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, self, Barkley, 0-54, high is poor, FV, <3 months FU) (follow-up 12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	49	-	8.23 lower (11.86 lower to 4.61 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self, Barkley, 0-27, high is poor, FV, <3 months PT) (follow-up 8-12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	52	-	1.36 lower (3.46 lower to 0.74 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self, Barkley, 0-27, high is poor, FV, <3 months FU) (follow-up 12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	49	-	2.97 lower (4.90 to 1.03 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self, Barkley, 0-27, high is poor, FV, <3 months PT) (follow-up 8-12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	52	-	3.63 lower (5.55 to 1.71 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self, Barkley, 0-27, high is poor, FV, <3 months FU) (follow-up 12 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40	49	-	5.26 lower (7.60 to 2.93 lower)	⊕OOO VERY LOW	CRITICAL
Responders by CGI (two point change in CGI-S, >3 months PT) (follow-up 15 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/16 (56.3%)	13.3%	RR 4.22 (1.08 to 16.45)	428 more per 1000 (from 11 more to 1000 more)	⊕⊕OO LOW	CRITICAL

Emotional dysregulation (observer, HAM-D, 0-53, high is worse, FV, >3 months PT) (follow-up 15 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	15	-	MD 5.56 lower (9.71 to 1.41 lower)	⊕⊕OO LOW	IMPORTANT
Emotional dysregulation (Self, BDI, 0-64, high is worse, FV, <3 months PT) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34	34	-	MD 5.62 lower (9.85 to 1.39 lower)	⊕OOO VERY LOW	IMPORTANT
Emotional dysregulation (Self, BDI, 0-64, high is worse, FV, <3 months FU) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	29	-	MD 8.10 lower (11.72 to 4.43 lower)	⊕⊕OO LOW	IMPORTANT
Behaviour/function (Self-rated, RATE antisocial scale, unclear range, high is worse, FV, <3 months PT) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	35	-	MD 1.05 lower (1.99 to 0.11 lower)	⊕OOO VERY LOW	CRITICAL
Behaviour/function (Self-rated, RATE antisocial scale, unclear range, high is worse, FV, <3 months FU) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	32	-	MD 2.43 lower (3.97 to 0.89 lower)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 78: Clinical evidence profile: Medication + CBT/DBT versus Medication + NSST for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Medication + CBT/DBT**	**Medication + NSST**	**Relative (95% CI)**	**Absolute**		
QoL (QLESQ, unclear scale, high is better, FV, >3 months PT) (follow-up 12 weeks; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	17	-	MD 33.10 higher (35.83 lower to 102.03 higher)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, self, ADHD-RS, high is worse, FV, 0-54, >3 months PT) (follow-up 12-15 weeks; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	56	54	-	SMD 0.33 lower (0.7 lower to 0.05 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (total, self, ADHD-RS, high is worse, FV, 0-54, >3 months FU) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	38	32	-	MD 3.58 lower (6.34 to 0.82 lower)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (hyperactivity, self, CAARS, high is worse, FV, 0-27, >3 months PT) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	17	-	MD 1.72 higher (4.41 lower to 7.85 higher)	⊕OOO VERY LOW	CRITICAL
ADHD symptoms (inattention, self, CAARS, high is worse, FV, 0-27, >3 months PT) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	17	-	MD 1.35 higher (4.62 lower to 7.32 higher)	⊕OOO VERY LOW	CRITICAL
CGI-I responders (>3 months PT) (follow-up 15 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/41 (53.7%)	24.3%	RR 2.21 (1.17 to 4.16)	294 more per 1000 (from 41 more to 768 more)	⊕OOO VERY LOW	CRITICAL
Emotional dysregulation (Self, BDI, 0-63, high is worse, FV, >3 months PT) (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15	17	-	MD 1.24 lower (9.37 lower to 6.89 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

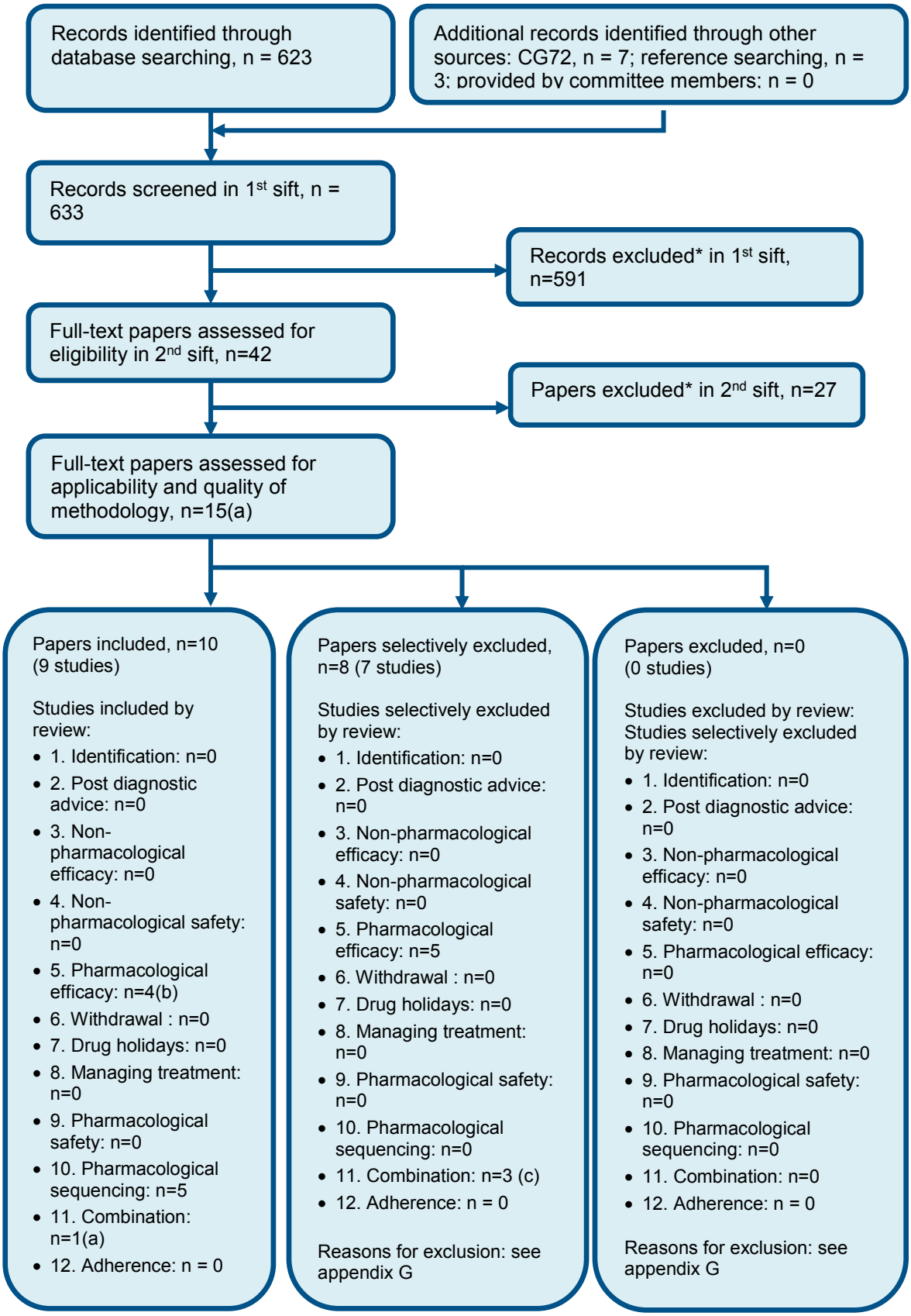
- **COMBINATION versus NOTHING/USUAL CARE**

Table 79: Clinical evidence profile: Stimulants + CBT/DBT versus NSST for ADHD in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stimulants + CBT/DBT	NSST alone	Relative (95% CI)	Absolute		
ADHD symptoms (total, self, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	103	-	MD 2.70 lower (4.45 to 0.95 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (total, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	103	-	MD 2.60 lower (4.49 to 0.71 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (hyperactivity, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	103	-	MD 2.20 lower (4.02 to 0.38 lower)	⊕⊕OO LOW	CRITICAL
ADHD symptoms (inattention, observer, CAARS, 0-30, high is worse, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	103	-	MD 2.50 lower (4.32 to 0.68 lower)	⊕⊕OO LOW	CRITICAL
Emotional dysregulation (Self, BDI, 0-63, high is poor, FV, >3 months PT) (follow-up 52 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	103	-	MD 1.20 lower (3.3 lower to 0.9 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
(a) note that there were 2 original models from the previous guideline (either included or excluded) which is why the numbers add to more than 15.
(b) Two articles identified were applicable to Q5 and Q10, for the purposes of this diagram it has been included under Q5 only.
(c) One of these is a model from the previous guideline that was exclude. Two articles identified were applicable to both Q5 and Q11 and have only been included here under Q11. One paper here was selectively excluded in Q11 but included in Q5 and so is double counted in this flowchart.

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 80: Studies excluded from the clinical review

Study	Exclusion reason
Abbasi 2011[2]	Incorrect intervention
Aman 2009[5]	Incorrect stratum
Aman 2014[4]	Incorrect population. Sequencing
Arnold 2015[6]	Incorrect population. Sequencing
Babinski 2014[7]	Incorrect study design
Babinski 2014[8]	Incorrect study design
Fabiano 2007[14]	Incorrect duration
Farmer 2012[15]	No usable outcomes
Farmer 2015[16]	Incorrect population. Sequencing
Foster 2007[18]	Incorrect stratum. Unusable outcomes
Gallucci 2006[19]	Incorrect study design
Helseth 2015[22]	No useable outcomes
Heriot 2008[23]	Incorrect study design
Janssen 2016[27]	No relevant outcomes
Kang 2011[30]	No usable outcomes
Konstenius 2010[33]	Incorrect intervention
Meisel 2013[40]	Incorrect intervention
Mesler 2016[42]	Incorrect stratum. Incorrect interventions
Pelham 2014[47]	Incorrect duration
Pelham 2016[48]	Inappropriate comparison
R.g. klein 1997[32]	Inappropriate diagnosis
Schachar 1997[53]	Incorrect intervention
Tamm 2012[60]	No usable outcomes
Warden 2012[64]	No usable outcomes

I.2 Excluded health economic studies

Table 81: Studies excluded from the health economic review

Reference	Reason for exclusion
Lord & Paisley 2000[39]	This study was assessed as not applicable, because the cost year (2000) is prior to a 15 year cut-off that the guideline employs for economic evaluations. It is also not using QALYs (cost per SMD in the SNAP-IV score)
Zupancic 1998[69]	This study was assessed as not applicable because of the perspective (Canadian third party payer). The cost year was also before the guideline date cut-off (1997). The outcome is also not QALYs (Change in Conners' teacher rating scale)
The MTA Co-operative study Jensen et al., 2005 Foster et al., 2007[29, 18]	This study was assessed as not applicable because it is a US study and there may be more applicable evidence. The date of costs is also before the guideline date cut-off (2001). The outcomes are also not in QALYs (cost per 'normalised' child, and cost per change on

Reference	Reason for exclusion
	CIS-ES).
King 2006[31]	This study was assessed as not applicable because of methodological limitations as the RCT that clinical effectiveness of combination therapy was based on a study that has been excluded from the guideline clinical review.
CG72 model[45]	The previous guideline model on children comparing combination treatments has been selectively excluded because it is not applicable as it is based on clinical evidence that is excluded from the clinical review.

Appendix J: Research recommendations

J.1 Combination in children under 5

Research question: What is the clinical and cost effectiveness of pharmacological vs non-pharmacological treatment versus a combination in children under 5 with ADHD?

Why this is important:

Many children are diagnosed with ADHD under the age of 5 years. There is much hesitancy around the use of ADHD medication in this age group, although there has been little research into the option. There is more evidence in this age group supporting the efficacy of non-pharmacological interventions (for example parent- training programmes), but there is no evidence directly comparing the efficacy of this with pharmacological treatment or a combination of the two.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Children under the age of 5 with ADHD and their parents or carers Intervention(s): Pharmacological treatment (e.g. methylphenidate, lisdexamfetamine, atomoxetine or guanfacine), non-pharmacological treatment (e.g. parent-training programmes), combination Comparison: Each other (3 arm study) Outcome(s): Quality of life, ADHD symptoms (total, inattention, hyperactivity) assessed by neutral observer and reported as continuous and dichotomous responder outcomes, medication use, behavioural measures, discontinuations, serious adverse events
Importance to patients or the population	Either support or reject the concept of medication use in this age group
Relevance to NICE guidance	Allow for evidence based recommendations on the use of medication or a combination of medication and parent-training programmes in this age group
Relevance to the NHS	Provide framework for guidance around prescribing in this age group
National priorities	NICE ADHD guideline
Current evidence base	There are a small number of studies comparing medication with placebo in this age group, a larger evidence based comparing parent-training programmes with usual care in this age group and no studies comparing the two head to head or in combination There is a lack of evidence measuring the long term effects of treatments for ADHD. As a chronic lifelong condition it is imperative trials have longer follow up measuring the benefits and risks of treatments.
Equality	Research could allow for recommendations tailored to age and not based on consensus and extrapolation from older children
Study design	RCT
Feasibility	Ethics of randomising children in this age group to medication or not are challenging but without RCTs in this population, difficult to recommend an appropriate strategy
Other comments	N/A
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

J.2 Combination in over 5s

Research question: What is the clinical and cost effectiveness of pharmacological vs non-pharmacological treatment versus a combination in children, young people and adults over 5 with ADHD?

Why this is important:

The question of the direct head to head comparisons between pharmacological and non-pharmacological treatment or a combination of the two in children, young people and adults over 5 with ADHD is critical to treatment decisions. There are many small studies looking at a variety of specific interventions under this heading but a paucity of large, well conducted RCTs of the kind that would be required for stronger recommendations and more useful information for patients.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Children, young people and adults over the age of 5 with ADHD and their parents or carers (if applicable), ideally treatment naïve but if not, to aid recruitment, then results should be stratified by previous treatment and response Intervention(s): Pharmacological treatment (e.g. methylphenidate, lisdexamfetamine, atomoxetine or guanfacine), non-pharmacological treatment (e.g. parent-training programmes in children, CBT in young people and adults), combination Comparison: Each other (3 arm study) Outcome(s): Quality of life, ADHD symptoms (total, inattention, hyperactivity) assessed by neutral observer and reported as continuous and dichotomous responder outcomes, medication use, behavioural measures, discontinuations, serious adverse events
Importance to patients or the population	Would provide better information on relative efficacy of these treatments to allow people to make more informed choices between options
Relevance to NICE guidance	Allow for stronger evidence based recommendations on the use of medication or a combination of medication and non-pharmacological treatments
Relevance to the NHS	Provide framework for guidance around prescribing in this age group
National priorities	NICE ADHD guideline
Current evidence base	There are a large number of small studies comparing these interventions however there is a wide range of baseline population characteristics and precise interventions involved (particularly in terms of non-pharmacological interventions) that makes it difficult to draw conclusions from their meta-analysis There is a lack of evidence measuring the long term effects of treatments for ADHD. As a chronic lifelong condition it is imperative trials have longer follow up measuring the benefits and risks of treatments.
Equality	Research could allow for recommendations tailored to age and not based on consensus and extrapolation from older children
Study design	RCT
Feasibility	Key issue is that study needs to be large enough to be adequately powered and not to be another small comparison that does not fit in readily with previous evidence
Other comments	N/A
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.