

Attention deficit hyperactivity disorder (update)

**[C] Evidence reviews for pharmacological
efficacy and sequencing pharmacological
treatment**

NICE guideline CG72

Intervention evidence review

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Draft for Consultation

*This evidence review was developed by
the National Guideline Centre*

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Contents

1	Pharmacological treatment.....	6
	Introduction	6
1.1	Review question: What is the most clinically and cost-effective pharmacological treatment for people with ADHD?	7
1.1.1	PICO table	7
1.1.2	Methods and process.....	8
1.1.3	Clinical evidence	9
1.1.4	Economic evidence.....	101
1.1.5	Resource impact.....	111
1.1.6	Evidence statements.....	111
1.2	Review question: What is the most clinically and cost-effective sequence of pharmacological treatment for children and young people and adults with ADHD?	120
1.2.1	PICO table	120
1.2.2	Methods and process.....	122
1.2.3	Clinical evidence	123
1.2.4	Economic evidence.....	139
1.2.6	Resource impact.....	149
1.2.7	Evidence statements.....	150
1.3	Recommendations	151
	Appendices.....	223
	Appendix A: Review protocols	223
	A.1 Pharmacological efficacy	223
	A.2 Pharmacological sequencing	228
	Appendix B: Literature search strategies	234
	B.1 Clinical search literature search strategy	234
	B.2 Health Economics literature search strategy.....	238
	Appendix C: Clinical evidence selection.....	243
	C.1 Pharmacological efficacy	243
	C.2 Pharmacological sequencing.....	244
	Appendix D: Clinical evidence tables	246
	D.1 Pharmacological efficacy	246
	D.2 Pharmacological sequencing.....	508
	D.2.1 Pre-School children (under 6 years of age)	509
	D.2.2 Children and young people (6-18 years old).....	509
	D.2.3 Adults.....	523
	Appendix E: Forest plots.....	526
	E.1 Pharmacological efficacy	526
	E.1.1 Children under the age of 5.....	526

E.1.2 Children and adolescents (aged 5 to 18).....	529
E.1.3 Adults.....	565
E.2 Pharmacological sequencing.....	585
E.2.1 Methylphenidate versus placebo in children with ADHD not responding to atomoxetine.....	585
E.2.2 Lisdexamfetamine dimesylate versus placebo in children with ADHD who had not responded to previous methylphenidate treatment.....	585
E.2.3 Lisdexamfetamine dimesylate versus atomoxetine in children with ADHD who had an inadequate response to previous methylphenidate treatment.....	585
E.2.4 Guanfacine AM versus placebo in children with ADHD are taking CNS stimulants but have a partial or suboptimal response	586
E.2.5 Guanfacine PM versus placebo in children with ADHD are taking CNS stimulants but have a partial or suboptimal response	587
E.2.6 Clonidine versus placebo in children with ADHD and insufficient response to stimulant treatment	588
E.2.7 Risperidone versus placebo in children with ADHD who do not show sufficient clinical response to methylphenidate.....	589
E.2.8 Guanfacine versus placebo in adults with a sub-optimal response to CNS stimulants	591
Appendix F: GRADE tables	592
F.1 Pharmacological efficacy	592
F.1.1 Pre-school children (under the age of 5)	592
F.1.2 Children and young people (aged 5 to 18)	594
F.1.3 Adults.....	627
F.2 Pharmacological sequencing.....	643
F.2.1 Pre-school children (under the age of 5)	643
F.2.2 Children and young people (aged 5 to 18)	643
F.2.3 Adults.....	651
Appendix G: Health economic evidence selection.....	653
Appendix H: Health economic evidence tables	656
H.1 Pharmacological efficacy	656
H.2 Pharmacological sequencing.....	667
Appendix I: Excluded studies.....	685
I.1 Excluded clinical studies.....	685
I.1.1 Pharmacological efficacy	685
I.1.2 Pharmacological sequencing	698
I.2 Excluded health economic studies.....	710
I.2.1 Pharmacological efficacy	710
I.2.2 Pharmacological sequencing	711
Appendix J: Research recommendations	712

1 Pharmacological treatment

2 Introduction

3 Immediate release (IR) stimulant medications, methylphenidate (MPH) and dexamfetamine
4 (DEX) have been used in the treatment of ADHD since the 1960s. From the mid-1990s the
5 level of drug prescribing for ADHD increased markedly in the UK, coinciding initially with
6 changes in the regulatory framework, and in the early-2000s with the introduction of modified
7 release (once or twice daily) methylphenidate preparations (Concerta XL®, Delmosart®,
8 Equasym XL®, Matoride XL®, Medikinet XL®, Xenidate XL®) and the non-stimulant,
9 atomoxetine (Strattera®). Recently, a once-daily preparation of lisdexamfetamine (Elvanse
10®, a pro-drug of dexamfetamine) and guanfacine ER (Intuniv®) have been introduced. At the
11 time of writing this guideline, drugs licensed in the UK for the treatment of ADHD in children
12 aged 6 years and over include: immediate and modified release methylphenidate and
13 dexamphetamine preparations, atomoxetine and modified-release guanfacine.

14 This picture is further complicated in that few drugs are licensed in the UK for the initiation of
15 treatment in adults that have received a new diagnosis of ADHD. One lisdexamfetamine
16 preparation (Elvanse adult®) is licensed for use in newly diagnosed adults, atomoxetine is
17 licensed for use in adults if the presence of symptoms of ADHD in childhood are confirmed
18 and some methylphenidate preparations (Concerta XL®, Delmosart®, Matoride XL®,
19 Medikinet XL®, Xiggitin XL®, Xenidate XL®) are licensed for continuation of treatment from
20 childhood or adolescence.

21 Despite a large treatment literature supporting the short-term benefits of stimulant medication
22 in children with ADHD, uncertainty still surrounds the quality of evidence and the balance of
23 risks and benefits of long-term drug treatment for ADHD in children and young people.
24

25 In adults the evidence base is far smaller and there are more unanswered questions.
26 Although stimulants are the most studied treatment for ADHD, their use in adults is still
27 limited. It remains an anomaly that many drugs that are considered to be safe and effective
28 in children and young people are not licensed for use in adults.
29

30 Key unanswered questions for clinicians treating all age groups concern the best sequence
31 of medications to use, the optimum duration of treatment, when it is appropriate to consider
32 drug discontinuation, which drug treatments to use in the presence of co-occurring conditions
33 and how and when to combine pharmacological and non-pharmacological interventions.
34 Important questions also relate to safety issues with ADHD medications, monitoring and
35 review as well as the balance of risks and benefits of ADHD drug treatment in less well
36 studied groups such as pre-school children, those with co-occurring mental and physical
37 health conditions, neurodevelopmental disorders, or learning disabilities.

38 The aim of this review, is to evaluate the evidence for the clinical and cost effectiveness of
39 the pharmacological management of children, young people and adults with ADHD. There
40 are two reviews; the first, evaluating the most clinically and cost effective pharmacological
41 treatment for people with ADHD and the second explores the most clinically and cost-
42 effective sequence of pharmacological treatment for children and young people and adults
43 with ADHD. This review should be read alongside the reviews on adverse events,
44 combinations of pharmacological and non-pharmacological treatments for the evidence on
45 when to decide on which treatment approach to take (for more information, see evidence
46 report E on adverse events and evidence report F on combination treatment).
47

1 **1.1 Review question: What is the most clinically and cost-**
2 **effective pharmacological treatment for people with ADHD?**

3 **1.1.1 PICO table**

4 For full details see the review protocol in appendix A.

5 **Table 1: PICO characteristics of review question**

Population	Children, young people and adults with ADHD Stratification: children under 5, aged 5 to 18 and adults over 18
Interventions	The following treatments (all doses), received for a minimum of 2 weeks: <ul style="list-style-type: none"> • Methylphenidate • Methylphenidate modified release • Dexamphetamine • Lisdexamfetamine dimesylate • Atomoxetine • Guanfacine • Clonidine • Tricyclic antidepressants • SSRIs • SNRIs • MAOIs • Risperidone • Olanzapine • Clozapine • Haloperidol • Quetiapine • Aripiprazole • Carbamazepine • Valproate • Lamotrigine • Lithium • Asenapine • Buspirone • Bupropion • Nicotine • Modafinil • Melatonin • Sativex • Acetylcholinesterase inhibitors • Antiparkinson medication • Combinations of the above <p>Not all of these medicines have a license for the treatment of ADHD, see individual summary of product characteristics for more information.</p>
Comparisons	Placebo Compared against each other Class vs. class comparisons will also be included

Outcomes	All outcomes will be separated into short term (up to 3 months) and long-term (>3 months) timepoints. Where multiple timepoints are reported within each definition, the longest timepoint only will be extracted. Critical <ul style="list-style-type: none">• Quality of life [continuous]• ADHD symptoms [continuous]• Clinical Global Impressions scale (improved or much improved) [dichotomous] Important <ul style="list-style-type: none">• Serious adverse events (all) [dichotomous]• Behavioural (children)/Functional (adults) measures [continuous]• Emotional dysregulation [continuous]• Academic outcomes (children) [continuous]• Substance use (alcohol and drug use) [dichotomous]• Self-harm [dichotomous]
Study design	Blinded RCTs and systematic reviews of RCTs

1 1.1.2 Methods and process

2 This evidence review was developed using the methods and process described in
3 Developing NICE guidelines: the manual.⁴⁷³ Methods specific to this review question are
4 described in the review protocol in appendix A.

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

6 This review sought to evaluate the clinical and cost effectiveness of pharmacological
7 interventions to treat ADHD. The population of this review was stratified by age (children
8 aged under 5 years, children and young people (5-18 years), and adults (over 18) as the
9 guideline committee believed that the effectiveness of pharmacological treatment would vary
10 between these populations and some outcomes were relevant for only one of the age strata.

11 Studies were excluded if they selected for a population exclusively on the basis of response
12 to the drug under investigation, for example if the inclusion criteria were 'previously used and
13 responded to methylphenidate' and the study compared methylphenidate with placebo.

14 A number of Cochrane reviews were identified which evaluated the effectiveness of
15 pharmacological treatments for people with ADHD^{144, 511, 512, 519, 626, 627}. As all of the reviews
16 included some studies that did not match the review protocol (for example, treatments not on
17 the protocol, studies that included only known responders), no review was fully included.
18 Rather, the references of each review were checked, and the data from relevant studies
19 were independently extracted and assessed for quality.

20 A network meta-analysis was considered for this question but deemed inappropriate due to
21 concerns over differences in trial populations, exact trial interventions and insufficient data
22 available for the relevant outcomes (see the methodology chapter for further details).

1 1.1.3 Clinical evidence

2 1.1.3.1 Included studies (children under the age of 5)

3 Four RCTs were included in the review^{41,274,290,539} that evaluated the effectiveness of
4 pharmacological treatments in pre-school age children (under 5 years of age); these are
5 summarised in Table 2 below.

6 Two studies compared the effectiveness of methylphenidate versus placebo^{146,274}, one study
7 compared risperidone versus placebo⁴¹, while the other compared risperidone versus
8 standard treatment⁵³⁹. One of these studies⁴¹ did not state whether any children included in
9 the sample had previously received medication. The other studies included both stimulant
10 naïve children and children that had previously received psychotropic medication^{146,274}. The
11 last study compared risperidone to standard treatment had both groups receiving
12 methylphenidate⁵³⁹. Evidence from these studies is summarised in the clinical evidence
13 summary tables below (Table 5, Table 6 and Table 7).

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

16 1.1.3.2 Excluded studies

17 See the excluded studies list in appendix I.

18 1.1.3.3 Summary of clinical studies included in the evidence review (children under 19 the age of 5)

20 **Table 2: Summary of studies included in the evidence review for pre-school children**

Study	Intervention and comparison	Population	Outcomes	Comments
Arabgol 2015 ⁴¹	Intervention: Risperidone 2mg/d in two divided doses (n=20) Comparison: Methylphenidate 20mg/d in two divided doses (n=18)	Pre-school children aged 3-6 years who met DSM-IV-TR criteria for ADHD. (n=38)	ADHD symptoms (ADHD-RS) at 6 weeks Discontinuation due to adverse events at 6 weeks	All/mixed subtypes (57.57% combined, 33.33% hyperactive/impulsive, 9.09% inattentive). Total scores parent ADHD-RS approximately 28. Baseline scores of ADHD-RS show the majority of the population had moderate ADHD.
Ghuman 2009 ²⁷⁴	Intervention 1: CNS stimulants – Methylphenidate initiated at 1.25mg t.i.d. and titrated based on response and tolerance Intervention 2: placebo Crossover trial (n=17)	Children aged 3 to 5 years who met the DSM-IV criteria for autistic disorder, Asperger disorder, or pervasive development disorder. Subjects were included only if they exhibited impairing symptoms of	ADHD symptoms (Conners parent rating scale) at 4 weeks Behaviour outcomes at 4 weeks	Mixed line. 8 children were drug naïve and 6 had received previous psychotropic medication. Mean baseline scores of 34.86 on CPRS

Study	Intervention and comparison	Population	Outcomes	Comments
		hyperactivity and impulsivity in multiple settings, and met severity criteria based on the Hyperactive-Impulsive subscale T-score of 65, 1.5(SD) on the CPRS or CTRS.		
Greenhill 2006 ²⁹⁰ (PA TS study)	Methylphenidate multiple doses (n=165) Comparison: placebo (n=165)	Children aged 3 to 5.5 years that met the DSM-IV criteria for ADHD	Treatment response at 4 weeks (SNAP-IV)	Children were stimulant naïve but had all undergone non-pharmacological treatment (parent-training programme) and been through a crossover methylphenidate trial immediately prior to the parallel phase whose efficacy results are included here
Safavi 2016 ⁵³⁹	Risperidone initiated at 1.25 mg/day and increased by 0.25-0.5mg each week to a maximum of 2mg/day + methylphenidate (n=21) Comparison: Methylphenidate alone (n=21)	Children aged 3 – 6 years that met the DSM-IV criteria for ADHD	ADHD symptoms – total, inattention, hyperactivity CGI-I Behaviour outcomes Discontinuation due to adverse events Serious adverse events All reported at PT 6 weeks.	Both groups were given methylphenidate. Methylphenidate was started at a dose of 2.5 mg twice daily and was increased 2.5-5mg each week based on the treatment response and the patients tolerance, to a maximum of 20/day.

1 See appendix D for full evidence tables.

2 **1.1.3.4 Included studies (children and young people aged 5 to 18)**

3 70 RCTs were included in the review^{3, 25, 35, 45, 62, 67, 87, 89, 95, 100, 118, 129, 142, 167, 172, 177, 178, 181, 198, 200}
4 ,202, 208, 234, 259, 266, 271, 292, 308, 315, 340, 345, 346, 350, 361, 366, 378, 389, 390, 429, 449, 451, 455, 456, 459, 468, 470, 475, 478, 490
5 ,502, 538, 545, 552, 553, 575, 576, 589, 591, 597, 614, 630, 632, 638, 646, 656, 657, 671, 694, 701, 711 that evaluated the
6 effectiveness of pharmacological treatments in children and young people (5-18 years of
7 age); these are summarised in Table 3 below. The following comparisons were included in
8 the review:

- 9
- 10 • eight RCTs compared immediate release methylphenidate versus placebo^{172, 178, 292}
11 ,490, 502, 575, 632, 701,
 - 12 • four RCTs compared osmotic-release oral system methylphenidate versus placebo³
,167, 234, 475

- 1 • one RCT compared immediate release methylphenidate versus extended release
2 methylphenidate ⁷⁰¹
- 3 • one RCT compared lisdexamfetamine versus placebo ¹⁶⁷
- 4 • one RCT compared methylphenidate versus lisdexamfetamine ¹⁶⁷
- 5 • 26 RCTs compared atomoxetine with placebo ^{25, 45, 62, 100, 118, 200, 202, 208, 266, 271, 308, 315, 340}
6 ,366, 390, 429, 449, 451, 459, 475, 591, 597, 614, 656, 657, 671
- 7 • two RCTs compared atomoxetine versus methylphenidate ^{475, 646}
- 8 • one compared atomoxetine versus guanfacine extended release ³⁴⁰
- 9 • one RCT compared guanfacine versus placebo ⁵⁵²
- 10 • eight RCTs compared guanfacine extended release versus placebo ^{89, 181, 340, 378, 478, 545}
11 ,553, 694
- 12 • Four RCTs compared clonidine versus placebo ^{350, 490, 576, 632}
- 13 • one RCT compared clonidine versus methylphenidate ⁴⁹⁰
- 14 • one RCT compared clonidine versus desipramine ⁵⁷⁶
- 15 • one RCT compared clonidine versus carbamazepine ⁴⁷⁰
- 16 • two RCTs compared desipramine versus placebo ^{576, 589}
- 17 • one RCT compared venlafaxine versus methylphenidate ⁷¹¹
- 18 • three RCTs compared risperidone versus placebo ^{129, 346, 468}
- 19 • one RCT compared aripiprazole versus placebo ⁶³⁰
- 20 • one RCT compared buspirone versus placebo ¹⁹⁸
- 21 • two RCTs compared buspirone versus methylphenidate ^{198, 458}
- 22 • two RCTs compared bupropion with placebo ^{142, 177}
- 23 • two RCTs compared bupropion versus methylphenidate ^{67, 345}
- 24 • three RCTs compared modafinil versus placebo ^{95, 361, 538}
- 25 • one RCT compared modafinil versus methylphenidate ³⁵
- 26 • one RCT compared melatonin versus placebo ⁶³⁸
- 27 • one RCT compared amantadine versus methylphenidate ⁴⁵⁶
- 28 • two RCTs compared clonidine and methylphenidate combined versus
29 methylphenidate monotherapy, clonidine monotherapy and placebo monotherapy ⁴⁹⁰
30 ,632
- 31 • one RCT compared atomoxetine versus fluoxetine versus atomoxetine. ³⁸⁹

32 Evidence from these studies is summarised in the clinical evidence summary tables below
33 (Table 8, Table 9, Table 10, Table 11, Table 14, Table 15, Table 16, Table 17, Table 11,
34 Table 12, Table 18, Table 19, Table 20, Table 21, Table 22, Table 23, Table 24, Table 25,
35 Table 26, Table 27, Table 28, Table 29, Table 30, Table 31, Table 32, Table 33, Table 34,
36 Table 35 and Table 36).

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

39 **Table 3: Summary of studies included in the review for children and young people**

Study	Intervention and comparison	Population	Outcomes	Comments
Abikoff 2009 ³	Intervention: osmotic release oral system (OROS) methylphenidate (mean dose 48.3mg) Comparison: Placebo Crossover trial	Children aged 8 to 13 years who met the DSM-IV criteria for ADHD	ADHD symptoms (SNAP-IV parent and teacher rated) at 4 weeks	All children stimulant naïve ADHD-RS scores 1.5SDs above gender and age norms 58% inattentive subtype; the rest

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=19)			unspecified
Allen 2005 ²⁵	Intervention: Atomoxetine 0.5mg/kg per day to 1.5mg/kg per day (n=76) Comparison: Placebo (n=72)	Children aged 7 to 17 years that met DSM-IV criteria for ADHD and had concurrent Tourette's syndrome or chronic motor tic disorder. (n=148)	ADHD symptoms (ADHD Rating Scale) at 18 weeks Discontinuation due to adverse events at 18 weeks	68.2% had previous stimulant exposure ADHD-RS scores 1.5SDs above gender and age norms. 60.8% combined subtype, 35.5% inattentive and 3.4% hyperactive/impu lsive. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Amiri 2008 ³⁵	Intervention: Modafinil 200- 300mg/day (n=30) Comparison: Methylphenidate 20mg/d if <30kg, 30mg/d if >30kg (n=30)	Children aged 6-15 years who were newly diagnosed with ADHD according to DSM- IV-TR criteria. (n=60)	ADHD symptoms (ADHD Rating Scale) at 6 weeks	Unclear line All subjects had combined subtype ADHD. ADHD-RS-IV school version scores >1.5SD above norms for age and gender. ADHD-RS-IV scores at baseline approximately 40 (parent) and 35 (teacher).
Anon 2002 ⁶³²	Intervention: Methylphenidate; mean dose 25.7mg/day (n=37) Intervention 2: Clonidine; mean dose 0.25mg per day (n=34) Intervention 3: Clonidine and methylphenidate combination; mean doses 0.25mg/day and 26.1mg/day (n=33)	Children aged 7 to 14 years who met the DSM-IV criteria for ADHD and Tourette's disorder, chronic vocal tic disorder or chronic motor tic disorder (n=136)	ADHD symptoms (Conners ASQ) at 16 weeks Discontinuation due to adverse events at 16 weeks	28% combined type; 70% inattentive; 2% hyperactivity subtype ADHD symptoms scores indicate the majority of participants had moderate ADHD. 58% of participants had previously used stimulants and 36% had prior

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison: Placebo (n=32)			use of clonidine
Arnold 2006 ⁴⁵	Intervention: Atomoxetine 0.3-0.4mg/kg/day Comparison: Placebo Crossover trial (n=16)	Children aged 5-15 years who met DSM-IV criteria for ADHD.	ADHD symptoms (DSM-IV) at 6 weeks Behavioural outcomes at 6 weeks	Subjects also had autism spectrum disorder. Subtype and previous medication status not stated. CGI-S 4.69 (SD 0.60). Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Bangs 2007 ⁶²	Intervention: Atomoxetine. target dose was 1.2mg/kg per day which could be increased to 1.8mg/kg (n=72) Comparison: Placebo (N=70)	Children and adolescents aged 12-18 who met DSM-IV criteria for ADHD (n=142)	ADHD symptoms (ADHD Rating Scale) at 9 weeks Dropped out due to adverse events at 9 weeks	79% had prior exposure to stimulants All subtypes (43% combined, 47% inattentive, 10% is hyperactive-impulsive) with severity over 1.5 SDs above ADHD-RS norms. ADHD-RS-IV score at least 1.5 SD above age and sex norms and a Children's Depression Rating Scale-Revised total score of 40 or more. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Barrickman 1995 ⁶⁷	Intervention: Bupropion 50-200mg/day Comparison: Methylphenidate 20-60mg/day Crossover trial (N =	Children aged 7-16 with a diagnosis of ADHD according to DSM-III-R	ADHD symptoms (Iowa-Conners Abbreviated Parent and Teacher Questionnaire) at 6 weeks Adverse events at 6 weeks	10 of 15 had previously taken Methylphenidate up to two weeks before enrolling. Results at seven weeks. Subtype status not stated. Subjects' CGI was

Study	Intervention and comparison	Population	Outcomes	Comments
	18)			“severe” in 12 and “moderate” in three.
Block 2009 ¹⁰⁰	Intervention: Atomoxetine (mean dose 1.25mg/kg per day) (n=195) Comparison: placebo (n=93)	Children aged 6 to 12 years who met the DSM-IV criteria for ADHD (n=288)	ADHD symptoms (ADHD-RS) at 6 weeks	75% combined subtype Severity: ADHD-RS score 1.5SDs above age and gender norms. Previous non-responders to atomoxetine or those with intolerable side effects were excluded. 30% had previously received stimulant treatment.
Biederman 2006 ⁹⁵	Modafinil. Titrated from 85mg to 425mg per day (n=197) Placebo (n=51)	Children 6 to 17 years with ADHD according to DSM-IV-TR criteria (n=248)	Clinical global impressions – improvement at 9 weeks Serious adverse events at 9 weeks Discontinuation due to adverse events at 9 weeks	Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher (“moderately ill” or worse). ADHD-RS-IV total and/or subscale score at least 1.5 SDs above normal values for age and gender 76% combined subtype, 20.6% inattentive subtype, 3.4% hyperactive-impulsive subtype Participants were stimulant naïve or had manifested an unsatisfactory response to stimulant therapy
Biederman 2007 ⁸⁷	Intervention: Lisdexamfetamine	Children aged 6 to 12 years who met	ADHD symptoms at 4 weeks	96% combined subtype

Study	Intervention and comparison	Population	Outcomes	Comments
(Childress 2014 ¹⁵⁵ , Lopez 2008 ⁴¹⁷)	dimesylate 30-70mg/day (n=218) Comparison: Placebo (n=72)	the DSM-IV criteria for ADHD (n=290)	Discontinuation due to adverse events at 4 weeks	ADHD-RS-IV scores of 28 or more Unclear line of treatment: previous non-responders were excluded
Biederman 2008 ⁸⁹	Interventions: Extended release guanfacine 2mg/d (n=87) Extended release guanfacine 3mg/d (n=86) Extended release guanfacine 4mg/d (n=86) Comparison: Placebo (n=86)	Children aged 6-17 who met DSM-IV criteria for a primary diagnosis of ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype (n=345)	ADHD symptoms (ADHD Rating Scale) at 5 weeks Clinical Global Impressions - Improvement scale at 5 weeks Behavioural outcomes at 5 weeks Discontinuation due to adverse events at 5 weeks	All/mixed subtypes (Inattentive 26.1%, Hyperactive-impulsive 2%, Combined 71.9%) All patients who received GXR began dosing at 1mg/day. GXR dosages were escalated weekly in 1mg increments beginning at 1mg/day at week 1 of the double blind treatment period with the highest dosages given during weeks 4 and 5. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Buitelaar 2001 ¹²⁹	Intervention: Risperidone 0.5mg BD initially, the dose could be increased to 1mg/day, max dose 5mg BD (n=19) Comparison: Placebo (n=19)	Adolescents aged 12-18 hospitalised due to a chronic pattern of repetitive aggressive behaviour with a DSM-IV diagnosis of conduct disorder, oppositional defiant disorder or ADHD, and below-average intelligence (n=38)	Behavioural outcomes at 6 weeks Serious adverse events at 6 weeks	70% naïve to psychotropics. 68% of the population had a comorbid diagnosis of ADHD. Subtype not stated. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Brown 2006 ¹¹⁸ ,	Intervention: Atomoxetine 0.8-	Children aged 8-12 with diagnosis of	ADHD symptoms (ADHD Rating	Allowed previous use of stimulant

Study	Intervention and comparison	Population	Outcomes	Comments
Weiss 2005 ⁶⁶²	1.8mg/kg/day (n=101) Comparison: Placebo (n=52)	ADHD confirmed by DSM-IV (n=153)	Scale) at 7 weeks Quality of life at 7 weeks	(60%) up to one week before enrolling. Results at six weeks. ADHD was classified as hyperactive/impulsive in one subject (1%), inattentive in 41 (27%), and combined in 111 (73%). ADHDRS-TV mean and SD was 65.6 (5.2) in active group and 64.4 (6.3) in control. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Casat 1987 ¹⁴² (Casat 1989 ¹⁴¹)	Intervention: Bupropion, max dose 150mg/day if 20-30kg, 200mg/day if 30-40kg and 250mg/day if >40kg (n=20) Comparison: Placebo (n=10)	Children aged 6-12 years who met DSM-III criteria for ADHD. (n=30)	ADHD symptoms (Conners Parent Teacher Questionnaire) at 6 weeks Clinical Global Impressions - Improvement Scale at 6 weeks Discontinuation due to adverse events at 6 weeks	87% of the population were stimulant naïve. All subjects were hyperactive subtype and scored >1.5 on the Hyperactive factor for the teacher, and >1.5 on the Impulsive-Hyperactive or Restless-Immature factors for the parent. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Coghill 2007 ¹⁷²	Intervention: Methylphenidate (0.6-1.2mg/kg per day) Comparison: Placebo Crossover trial (n=25)	Children aged 7 to 15 years who met the DSM-IV or ICD-10 criteria for ADHD	ADHD symptoms (Parent/Teacher Conners' Global Index) at 4 weeks Clinical global impressions (improvement) at 4 weeks	All participants drug naïve All participants combined subtype

Study	Intervention and comparison	Population	Outcomes	Comments
NCT00763971 trial: Coghill 2013 ¹⁶⁷ (Coghill 2014 ¹⁷¹ , Banaschewski 2013 ⁶¹ , Coghill 2014 ¹⁷⁰)	Intervention: Lisdexamfetamine dimesylate 30-70mg/day (n=111) Comparison: Methylphenidate 18-54mg per day (n=111) Comparison: placebo (n=110)	Children 6 to 16 years with ADHD according to DSM-IV-TR criteria (n=336)	ADHD symptoms (ADHD-RS) at 7 weeks Discontinuation due to adverse events at 7 weeks Clinical global impressions (improvement) at 7 weeks Academic outcomes at 7 weeks	ADHD-RS-IV score of 28 or higher 63% had previously been treated with ADHD medication; previous non-responders to OROS MPH excluded and those whose current ADHD medication provided effective control of their symptoms. 68.7% combined subtype
Conners 1980 ¹⁷⁸	Intervention: Methylphenidate, max dose 60mg/day (n=20) Comparison: Placebo (n=21)	Children aged 6-11 years with physician diagnosed hyperkinesia (n=60, 19 subjects in third group not relevant to protocol)	ADHD symptoms (Conners Parent Questionnaire) at 8 weeks	Unclear line of treatment
Conners 1996 ¹⁷⁷	Intervention: Bupropion, max dose of 150 mg/day if 20-30kg, 200mg/day if 31-40kg and 250mg/day if >40kg (n = 72) Comparison: Placebo (n = 37)	Children aged 6-12 years who met DSM-III criteria for ADHD (n=109)	ADHD symptoms (Conners Abbreviated Parent Questionnaire) at 6 weeks Discontinuation due to adverse events at 6 weeks	Unclear line of treatment. All subjects were required to have scores of at least 1.5 on the Conners Parent Questionnaire Hyperactive-Immature or Conduct Disorder factors, and the Hyperactive or Conduct Disorder factors from the Conners Teacher Questionnaire.
Connor 2010 ¹⁸¹	Intervention: Extended release guanfacine, max dose 4mg/day (n=138)	Children aged 6-12 years who met DSM-IV criteria for ADHD and oppositional	Discontinuation due to adverse events at 8 weeks	Unclear line of treatment. All subtypes (Inattentive (12.6%),

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison: Placebo (n=79)	symptoms. (n=217)		Hyperactive (3.3%), and Combined (84.1%). Subjects had a baseline score of 24 or more on the ADHD-RS-IV and a baseline score of 14 or more for males and 12 or more for females on the oppositional subscale of CPRS-R:L. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Davari-ashtiani 2010 ¹⁹⁸	Intervention: Buspirone maximum dose 45mg/d (n=18) Comparison: Methylphenidate maximum dose 60mg/d(n=16)	Children aged 6-12 years who met DSM-IV-TR diagnostic criteria for ADHD. (n=34)	ADHD symptoms (ADHD Rating Scale) at 6 weeks Serious adverse events at 6 weeks Discontinuation due to adverse events at 6 weeks	Drug naïve. All children diagnosed with combined ADHD subtype. Mean baseline severity scores on ADHD-RS was around 32 for parent and teacher. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
De Jong 2009 ²⁰⁰	Intervention: Atomoxetine 1.2mg/kg per day. Mean dose 1.11(0.12)mg/kg per day Comparison: Placebo Crossover trial: ADHD alone (n=16) ADHD and reading disorder (n=20)	Children aged 8 to 12 years who met DSM-IV criteria for ADHD and reading disorder. (n=36)	ADHD symptoms (ADHD Rating Scale) at 4 weeks Clinical global impressions – Improvement scale at 4 weeks	Unclear line All children diagnosed with combined subtype. Mean (and SD) ADHD-RS score in the ADHD alone group, was 37.8 (9.0), in the combined ADHD-RD group was 39.0 (9.1). Baseline scores of ADHD-RS show the majority of the population had

Study	Intervention and comparison	Population	Outcomes	Comments
Dell'agnello 2009 ²⁰²	Intervention: Atomoxetine 1.2mg/kg/d(n=105) Comparison: Placebo (n=32)	Children aged 6-15 years who met DSM-IV diagnostic criteria for ADHD and oppositional defiant disorder. (n=137)	ADHD symptoms (CARS ADHD index) at 8 weeks Discontinuation due to adverse events at 8 weeks	severe ADHD. 20% of the atomoxetine group and 12.5% of the placebo group had previous therapy. 89% of the population diagnosed with combined subtype.
Dittmann 2011 ²⁰⁸ , Wehmeier 2011 ⁶⁵⁵	Intervention: Atomoxetine max dose 1.2mg/kg (n=121) Comparison: Placebo (n=60)	Children aged 6-17 years who met DMS-IV criteria for ADHD (n=181)	ADHD symptoms (Swanson, Nolan, and Pelham Rating Scale-Revised) at 9 weeks Quality of life at 9 weeks	44% previously treated with a stimulant. 75% of the population diagnosed with combined subtype.
Findling 2008 ²³⁴	Intervention: OROS methylphenidate, max dose 54mg/day (n=91) Comparison: Placebo (n=85)	Children aged 6-12 years who met DMS-IV criteria for ADHD (n=274; n=98 in third arm not relevant to review)	Discontinuation due to adverse events at 5 weeks	85% drug naïve. 80.5% of the study population were of the combined subtype of ADHD, 17% of the inattentive subtype, 1.4% of the hyperactive/impulsive subtype and 1.06% of the unclassified subtype.
Gadow 2008 ²⁵⁹ (²⁶¹ , Gadow 2007 ²⁶⁰)	Intervention: IR Methylphenidate 0.1-0.5mg/kg per day Comparison: Placebo Crossover trial (n=31)	Children aged 6 to 12 years who met the DSM-III or DSM-IV criteria for ADHD	ADHD symptoms (Abbreviated teachers/parents rating scale, Conners rating scale) at 2 weeks	Subtype not stated 37% had previous history of medication for ADHD Mean score of 20.7 on Child Symptom Inventory (parent rated)
Gau 2007 ²⁶⁶	Intervention: Atomoxetine 1.2-1.8mg/kg/day, mean daily dose 43.12mg (n=72)	Children aged 6-16 years diagnosed with ADHD according to the DSM-IV. (n=106)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks Discontinuation due to adverse events at 6 weeks	64% drug naïve. Baseline scores of CGI-S show the majority of the population

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison: placebo (n=34)			had moderate ADHD. 73% combined subtype, 27% combined subtype, and no participants had the predominantly hyperactive subtype.
Geller 2007 ²⁷¹	Intervention: Atomoxetine, max dose 120 mg/day (n=87) Comparison: Placebo (n=89)	Children aged 8-17 years diagnosed with ADHD according to the DSM-IV. (n=176)	ADHD symptoms (ADHD - Rating Scale) at 12 weeks Discontinuation due to adverse events at 12 weeks	37.5% were stimulant naïve All subjects met DSM-IV criteria for ADHD and for at least one of the following anxiety disorders: separation anxiety disorder, generalised anxiety disorder, or social phobia. 75% were of the combined subtype, 23% inattentive and 1% hyperactive/impulsive.
Greenhill 2002 ²⁹²	(n=155) Intervention 1: CNS stimulants – Methylphenidate (maximum 60mg/day) (n=159) Intervention 2: No treatment - Placebo.	(n=321) Children aged 6 to 16 years diagnosed with ADHD according to DSM-IV criteria	Discontinuation due to adverse events at 3 weeks	Combined and predominantly hyperactive/impulsive subtypes only 64% had been previously treated for ADHD
Handen 2015 ³⁰⁸	Intervention 1: Atomoxetine (n=32), mean dose 49.8 (23.3) mg/ day. Intervention 2: Atomoxetine and parent training (n=32) Comparison: placebo (n=64)	Children aged 5 to 14 years who met the DSM-IV criteria for ADHD (n=128)	ADHD symptoms total at 10 weeks CGI-I at 10 weeks behaviour outcomes at 10 weeks	Severity: mixed
Harfterkamp 2012 ³¹⁵ ;	Intervention: Atomoxetine, fixed	Children aged 6 to 17 diagnosed with	ADHD symptoms (ADHD - Rating	37% received no previous drug

Study	Intervention and comparison	Population	Outcomes	Comments
Harfterkam p 2014 ³¹⁴	dose of 1.2mg/kg/day (n=48) Comparison: Placebo (n=49)	ADHD and ASD according to the DSM-IV. (n=97)	Scale) at 8 weeks Clinical global impressions - Improvement) at 8 weeks Discontinuation due to adverse events at 8 weeks	treatment All subjects scored over 1.5 SD above age-standard norms for ADHD-RS. Sub-type not stated. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Huss 2014 ³⁴⁰	Intervention 1: Guanfacine 4-7mg/day (n=115) Intervention 2: Atomoxetine 1.2mg/kg per day; mean dose 42.1(20.1)mg per day mean (n=112) Comparison: placebo (n=111)	Children aged 6 to 17 years who met the DSM-IV criteria for ADHD (n=338)	Clinical global impressions – improvement at 10 to 13 weeks ADHD symptoms (ADHD Rating Scale) at 10 to 13 weeks Discontinuation due to adverse events at 13 weeks	85% combined, 12% inattentive and 3% hyperactive impulsive Moderate severity (ADHD-RS score of 32 or higher at baseline) Unclear line of treatment
Jahangard 2017 ³⁴⁶	Intervention: Risperidone 0.5 mg/d (=42) Comparison: placebo (n=42)	Children aged 7 to 10 years who met the DSM-IV criteria for ADHD (n=84)	ADHD symptoms – inattention, hyperactivity Behaviour outcomes Emotional dysregulation All reported PT at 8 weeks	All participants were on methylphenidate (1 mg/kg/d), Ritalin, sustained.
Jain 2011 ³⁵⁰	Intervention: Clonidine (0.2mg/kg per day and 0.4mg/kg per day) (n=158) Comparison: Placebo (n=78)	Children 6 to 17 years with ADHD according to DSM-IV-TR criteria (n=236)	ADHD symptoms (ADHD rating scale) at 8 weeks Serious adverse events at 8 weeks Discontinuation due to adverse events at 8 weeks	Minimum score of 26 on ADHD-RS
Jafarinia 2012 ³⁴⁵	Intervention: Bupropion 100mg/d if <30kg, 150mg/d if >30kg(n=20) Comparison: Methylphenidate 20mg if <30kg, 30mg	Children and adolescents aged 6-17 who met the DSM-IV-TR diagnostic criteria for ADHD (n=44)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks Serious adverse events at 6 weeks Discontinuation due to adverse events at 6 weeks	All patients were drug naïve. All subjects scored over 1.5 SD above age-standard norms for ADHD-RS. Subtype diagnosis not

Study	Intervention and comparison	Population	Outcomes	Comments
	is >30kg (n=20)			stated. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Kahbazi 2009 ³⁶¹	Intervention: Modafinil 200mg is <30kg, 300mg if >30kg (n=23) Comparison: Placebo (n=23)	Children and adolescents aged 6-15 who met the DSM-IV diagnostic criteria for ADHD (n=46)	ADHD symptoms (ADHD - Rating Scale) at 5 weeks	New patients, implied drug naïve. All patients with combined subtype. ADHD-RS-IV total or subscale scores > 1.5SD compared to norms for age and gender. Mean baseline scores approximately 36. All subjects had combined-type ADHD. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Kelsey 2004 ³⁶⁶	Intervention: Atomoxetine. Maximum of 1.8mg/kg per day (n=133) Comparison: Placebo. (n=64)	Children aged 6-12 who met ADHD diagnostic criteria as defined by DSM-IV (n=197)	ADHD symptoms (ADHD - Rating Scale) at 8 weeks Discontinuation due to adverse events at 8 weeks	52.5% had previous stimulant exposure. Participants were required to have an ADHD-RS score of 1.5SDs above gender and age norms. 96% combined type, 28% inattentive, 3% hyperactive impulsive. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Kratochvil 2005 ³⁸⁹	Intervention: Atomoxetine 1.2mg/kg per day	Children aged 7-17 years old who met ADHD diagnostic	ADHD symptoms (ADHD-RS) at 8 weeks	All/mixed subtypes (77.3% combined,

Study	Intervention and comparison	Population	Outcomes	Comments
	and fluoxetine 20mg/day (n=127) Comparison: Atomoxetine 1.2mg/kg per day and placebo; (n=46)	criteria as defined by DSM-IV and comorbid depressive or anxiety symptoms (n=173) 45.7% of participants had major depression and 31.85% generalised anxiety disorders	Discontinuation due to adverse events at 8 weeks	20.7% inattentive and 2% hyperactive). Line of treatment unclear. ADHD-RS scores at least 1.5SDs above age and gender norms.
Kratochvil 2011 ³⁹⁰	Intervention: Atomoxetine 0-8-1.8mg/kg/d (n=51) Comparison: Placebo (n=50)	Children aged 5-6 years old who met ADHD diagnostic criteria as defined by DSM-IV (n=101)	ADHD symptoms (ADHD-RS) at 8 weeks Discontinuation due to adverse events at 8 weeks	All/mixed subtypes (82% combined). 18% of participants not drug naïve. Participants had mean total ADHD-RS scores were 38 (parent) and 36 (teacher) at baseline. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Kollins 2011 ³⁷⁸	Intervention 1: Extended release guanfacine 1-3 mg/day (n=121) Control: Placebo. (n=57)	Children and adolescents 6-17 meeting DSM-IV-TR ADHD criteria (n=178)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks Discontinued due to adverse effects at 6 weeks	Previous treatment allowed, proportion not stated. ADHD subtype not stated. All subjects had a baseline score of >24 on the ADHD-RS-IV and a baseline score > 4 on the CGI-S scale.
Martenyi 2010 ⁴²⁹	Intervention: Atomoxetine, titrated to a max dose of 1.8mg/kg/day (n=72) Comparison: Placebo (n=33)	Children and adolescents aged 6-16 who met the DSM-IV diagnostic criteria for ADHD (n=105)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks Serious adverse events at 6 weeks Discontinuation due to adverse events at 6 weeks	All participants were stimulant naïve, however 40% were on nootropics (n=30) or psychotropics (n=14) before the trial, and 10% continued another

Study	Intervention and comparison	Population	Outcomes	Comments
				medication during the trial. All ADHD subtypes were included, 72.4% combined, 24% inattentive, 5% hyperactive. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Michelson 2001 ⁴⁵¹ (Newcorn 2005) ⁴⁷⁷	Intervention: Atomoxetine 0.5mg/kg/d - 1.8mg/kg/d (n=213) Comparison: Placebo (n=84)	Children and adolescents aged 8-18 who met the DSM-IV diagnostic criteria for ADHD (n=297)	Quality of life at 13 weeks ADHD symptoms (ADHD - Rating Scale) at 13 weeks Clinical Global Impressions - Improvement scale at 13 weeks Behavioural outcomes at 13 weeks Discontinuation due to adverse events at 13 weeks	Unclear line of therapy. All/mixed subtypes. Participants scored 1.5 SDs above age and gender norms on ADHD RS. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Michelson 2002 ⁴⁴⁹	Intervention Atomoxetine. Maximum 1.5mg/kg per day. (n=85) Comparison: Placebo. (n=85)	Children aged 6-16 who met DSM-IV criteria for ADHD (n=170)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks Discontinuation due to adverse events at 6 weeks	55.3% had previous stimulant treatment. ADHD-RS-IV scores 1.5 above gender and age norms
Mohammedi 2010 ⁴⁵⁶	Intervention: Amantadine 100mg/d if <30kg, 150mg/d if >30kg (n=20) Comparison: Methylphenidate 20-30mg/d (n=20)	Children and adolescents aged 6-14 who met the DSM-IV diagnostic criteria for ADHD (n=40)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks	New patients, implied drug naïve. All patients with combined subtype. ADHD-RS-IV >1.5SD above general population. Mean ADHD-RS-IV subscales at baseline = ~15 (inattentive; parent) and 17 (hyperactivity/impulsivity; parent). Baseline scores

Study	Intervention and comparison	Population	Outcomes	Comments
				of ADHD-RS show the majority of the population had moderate ADHD.
Mohamma di 2012 ⁴⁵⁵	Intervention: Buspirone 20mg if <30kg, 30mg if >30kg (n=23) Comparison: Methylphenidate 20mg if <30kg, 30mg if >30kg(n=23)	Children and adolescents aged 6-14 years who met the DSM-IV diagnostic criteria for ADHD (n=46)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks	All patients drug naive. All patients had combined subtype of ADHD. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Montoya 2009 ⁴⁵⁹	Intervention: Atomoxetine 1.2mg/kg/d(n=100) Comparison: Placebo (n=51)	Children and adolescents aged 6-15 years who were newly diagnosed (\leq 3 months) with ADHD according to DSM-IV-TR (n=151)	ADHD symptoms (ADHD - Rating Scale) at 12 weeks	All patients drug naive. All/mixed subtypes (63.1% combined, 32.9% inattentive, 4% hyperactive). Mean total ADHD-RD-IV score (parent) = 39 at baseline. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Nagaraj 2006 ⁴⁶⁸	Intervention: Risperidone. No dosage details provided. (n=20) Comparison: Placebo (n=20)	Children up to 12 years of aged diagnosed with autism according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria (n=40)	Behavioural outcomes at 24 weeks	Unclear line. All/mixed subtypes were included.
Nair 2009 ⁴⁷⁰	Intervention: Clonidine 8 μ g/kg (n=25) Comparison: Carbamazepine. No dosage details provided. (n=25)	Children aged 4-12 years diagnosed with ADHD as per the DSM-IV criteria (n=50)	ADHD symptoms (Vanderbilt rating scale) at 4 weeks	Unclear line. The predominant subtype of ADHD was the combined type (55%). 15% of the study group also had conduct disorder, 12.5% had seizures, and 10% had ODD. Total

Study	Intervention and comparison	Population	Outcomes	Comments
				scores on Vanderbilt rating scale were approximately 45 at baseline.
Newcorn 2008 ⁴⁷⁵	Interventions: Atomoxetine, 0.8-1.8 mg/kg per day (n=82) OROS methylphenidate, 18-54 mg/day (n=82) Comparison: Placebo (n=27)	Children aged 6-16 diagnosed with ADHD as per the DSM-IV criteria (n=191)	Quality of life at 6 weeks ADHD symptoms (CPRS) at 6 weeks	Subpopulation of stimulant naive subjects
Newcorn 2013 ⁴⁷⁸ (Stein 2015 ⁵⁹⁸)	Intervention: Extended release guanfacine maximum dose 4mg/d (n=227) Comparison: Placebo (n=113)	Children aged 6-12 years diagnosed with ADHD as per the DSM-IV criteria (n=340)	ADHD symptoms (ADHD - Rating Scale) at 8 weeks Academic outcomes at 8 weeks	Unclear line. All/mixed subtypes (Predominantly inattentive subtype was an exclusion criteria). All participants had ADHD-RS-IV baseline score of 28 or more, and a CGI-S score of 4 or more.
Palumbo 2008 ⁴⁹⁰ (Cannon 2009 ¹³⁶ , Daviss 2008 ¹⁹⁹)	Interventions: Clonidine, maximum dose 0.6mg/day (n=31) Methylphenidate, maximum dose 60mg/day (n=29) Methylphenidate and clonidine combination (maximum doses 60mg/day and 0.6mg/day respectively) (n=32) Comparison: Placebo (n=30)	Children aged 7-12 who met the DSM-IV diagnostic criteria for ADHD (n=122)	ADHD symptoms (Conners ASQ-T) at 16 weeks Behavioural outcomes at 16 weeks Discontinuation due to adverse events at 16 weeks	An estimated 47% of participants had been previously treated with stimulants, and 7% had been previously treated with clonidine. Participants were required to have a CGAS score of less than 70 75% combined subtype, 18.8% inattentive, 6.2% hyperactive/impulsive. Approximately half of the population had comorbid ODD suggesting

Study	Intervention and comparison	Population	Outcomes	Comments
				moderate ADHD.
Pliszka 2000 ⁵⁰²	Intervention: Methylphenidate, 5-10mg BD-TDS (n = 20) Comparison: Placebo (n=18)	Children (mean age 8.1± 1.4 years) diagnosed with ADHD established using the Diagnostic Interview Schedule for Children (n=58; n=20 randomised to intervention not relevant to this review)	Clinical global impressions - Improvement scale at 3 weeks	21% had had prior stimulant treatment. All subjects had to be at least 1.5 SD above the mean for his/her age and sex on the IOWA CTRS I/O factor.
Rugino 2003 ⁸⁹⁸	Intervention: Modafinil, 200-300mg/day (n=11) Comparison: Placebo (n=11)	Children aged 5-15 who met DSM-IV for ADHD (n=22)	ADHD symptoms (ADHD - Rating Scale) at 6 weeks Discontinuation due to adverse events at 6 weeks	Unclear line All subjects had an average percentile score for the ADHD Rating Scale IV of 70 or higher
Sallee 2009 ⁵⁴⁵	Intervention: Guanfacine (n=258) All doses – 1, 2, 3 and 4mg/day. Comparison: Placebo (n=66)	Children and adolescents 6-17 meeting DSM-IV-TR ADHD criteria (n=324)	ADHD symptoms (ADHD Rating Scale) at 6 weeks Clinical global impressions – improvement at 6 weeks Discontinuation due to adverse events at 6 weeks	73% combined, 26% inattentive, 2% hyperactive/impulsive Severity: Mixed (Mean ADHD-RS-IV score of 40.1 (SD 8.65)) Unclear line of treatment
Scahill 2001 ⁵⁵²	Intervention: Guanfacine 0.5mg TDS (n=17) Comparison: Placebo (n=17)	Children aged 7-15 who met DSM-IV criteria for ADHD and DSM-IV criteria for tic disorder (n=34)	ADHD symptoms (ADHD - Rating Scale) at 8 weeks Clinical global impressions – Improvement scale at 8 weeks	30% of the population had had previous treatment. All subjects had to have a baseline score of 1.5 or more SD for age and gender on the 10 item conners hyperactivity index
Scahill 2015 ⁵⁵³	Intervention: Extended release guanfacine. Maximum 3mg (<25kg) and 4mg (>25kg). (n=30) Comparison: placebo (n=32)	Children aged 5-14 who met the DSM-IV diagnostic criteria for ADHD (n=62)	ADHD symptoms (ADHD - Rating Scale) at 8 weeks Behavioural outcomes at 8 weeks Serious adverse events at 8 weeks Discontinuation due to adverse events	Mixed line of treatment. A minimum score of 24 on the parent-rated Aberrant behaviour Checklist-hyperactivity subscale, a CGI-S score of

Study	Intervention and comparison	Population	Outcomes	Comments
			at 8 weeks	moderate or greater and an IQ of 35 (or mental age of 18 months) or greater. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Simonoff 2013 ³⁸⁵	Intervention: Methylphenidate 0.5mg, 1mg and 1.5mg/kg TDS (n=61) Comparison: Placebo (n=61)	Children aged 7-15 with a diagnosis of ICD-10 Hyperkinetic disorder and a full scale IQ of 3-69 (n=122)	ADHD symptoms (Conners ADHD index) at 16 weeks Discontinuation due to adverse events at 16 weeks	Unclear line
Singer 1995 ⁵⁷⁶	Interventions: Desipramine 25mg QDS Clonidine 0.05mg QDS Comparison: Placebo Crossover trial (n=34)	Children aged 7.2-13.6 diagnosed with ADHD as per the DSM-III criteria (n=34)	Behavioural outcomes at 6 weeks	All patients drug naive. Comorbidities tic disorder and Tourette's. Baseline scores of the child behaviour checklist show the majority of the population had severe ADHD.
Spencer 2002 ⁵⁹¹	Intervention: Atomoxetine. Maximum 2mg/kg per day (n=127) Comparison: Placebo (n=126)	Children diagnosed with ADHD as per the DSM-IV criteria (n=291; n=38 randomised to intervention with no reported data)	ADHD symptoms (ADHD - Rating Scale) at 9 weeks	All patients drug naive Patients were required to have a score on the ADHD-RS at least 1.5 SDs above the age and gender norms for their diagnostic subtype. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Spencer 2002 ⁵⁸⁹	Intervention: desipramine. 3.5mg/kg per day (n=21) Comparison:	Children diagnosed with ADHD as per the DSM-IV criteria. All subjects had a history of Tourette disorder or non-	ADHD symptoms (ADHD - Rating Scale) at 6 weeks	53.6% had received previous stimulants. Baseline scores of ADHD-RS

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=20)	Tourette disorder chronic tic disorders. (n=41)		show the majority of the population had severe ADHD.
Spencer 2008 ⁵⁹⁷	Intervention: Atomoxetine 0.5-1.5mg/kg per day (n=61) Comparison: Placebo (n=56)	Children aged 7 to 17 years who met the DSM-IV criteria for ADHD and Tourette's syndrome (n=117)	ADHD symptoms (ADHD-RS) at 8 weeks Discontinuation due to adverse events at 8 weeks	65.9% combined type; 31% inattentive; 4.1% hyperactivity subtype ADHD-RS scores 1.5SDs above age and gender norms 68.4% of participants had previously used stimulants.
Takahashi 2009 ⁶¹⁴	Intervention 1: Atomoxetine 0.5mg/kg per day (n=62) Intervention 2 Atomoxetine 1.2mg/kg per day (n=60) Intervention 3 Atomoxetine 1.8mg/kg per day (n=61) Comparison: placebo (n=62)	Children aged 6-17 diagnosed with ADHD as per the DSM-IV criteria (n=245)	ADHD symptoms (ADHD - Rating Scale) at 8 weeks Discontinuation due to adverse events at 8 weeks	46% stimulant naïve, 61.2% inattentive subtype, 34.2% combined, 4.5% hyperactive/impulsive. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Tramontina 2009 ⁶³⁰	Intervention: Aripiprazole 5 – 20mg/day (n=18) Comparison: Placebo (n=25)	Children aged 8-17 diagnosed with ADHD as per the DSM-IV criteria and DSM-IV bipolar 1 or 2 disorder (n=43)	ADHD (Swanson, Nolan, and Pelham Rating Scale-Revised) symptoms at 6 weeks	None of the patients had previously been treated with aripiprazole. All/mixed subtypes (79% of patients were of combined subtype of ADHD and 21% of either inattentive or hyperactive/impulsive subtype. Mean SNAP-IV score = 2.21 (intervention) and 2.02 (control); scale =

Study	Intervention and comparison	Population	Outcomes	Comments
				0-3. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Van der heijden 2007 ⁶³⁸	Intervention: Melatonin 3mg if <40kg, 6mg if > 40kg (n=54) Comparison: Placebo (n=53)	Children aged between 6-12, diagnosis of ADHD according to DSM-IV criteria and chronic sleep-onset insomnia (SOI) (n=107)	Quality of life at 4 weeks Behavioural outcomes at 4 weeks Discontinuation due to adverse events at 4 weeks	Unclear line of treatment. All/mixed subtypes (73% of patients were of combined subtype of ADHD, 21% of patients were of the inattentive subtype and 3.8% were of the hyperactive/impulsive subtype). Approximately half of the population had at least one psychiatric comorbidity suggesting moderate ADHD.
Wang 2007 ¹³¹	Intervention: Atomoxetine 0.8-1.8 mg/kg/day (n = 164) Comparison: Methylphenidate 0.2-0.6 mg/kg/day (n = 166)	Children and adolescents aged 6-16 years, weighing between 20 and 60 kg who met DSM-IV criteria for ADHD (n=330)	ADHD symptoms (ADHD Rating Scale) at 8 weeks Behavioural outcomes at 8 weeks Discontinuation due to adverse events at 8 weeks	24% had had previous exposure to stimulant treatment. All/mixed subtypes (59% of patients were of combined subtype of ADHD, 38% of patients were of the inattentive subtype and 3% were of hyperactive/impulsive subtype). Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Wehmeier 2012 ⁶⁵⁶	Intervention: Atomoxetine. Target	Children aged between 6-12,	ADHD symptoms (ADHD Rating	75.2% of the study population

Study	Intervention and comparison	Population	Outcomes	Comments
(Wehmeier 2015 ⁶⁵⁴ , Wehmeier 2014 ⁶⁵²)	dose 1.2mg/kg/day (n=63) Comparison: Placebo (n=62)	diagnosis of ADHD according to DSM-IV criteria (n=125)	Scale) at 8 weeks	were stimulant naive, previous treatment with atomoxetine was an exclusion criteria. 70.4% of the study population included patients with combined subtype of ADHD, 22.4% with predominantly inattentive subtype and 0.8% with predominantly hyperactive/impulsive subtype. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Wehmeier 2011 ⁶⁵⁷	(n=64) Intervention 1: CNS stimulants – Atomoxetine (1.2mg/kg per day) (n=64) Intervention 2: No treatment. Matching placebo.	(n=128) children aged 6 to 12 years who met the DSM-IV criteria for ADHD	Discontinuation due to adverse events at 8 weeks	Exclusion criteria: previous treatment with atomoxetine or other psychotropic medication other than the study drug
Wietecha 2013 ⁶⁶⁹ (Saylor 2009 ⁵⁵¹ Wietecha 2009 ⁶⁷¹)	Intervention: Atomoxetine 1.2mg/kg per day (n=120) Comparison: Placebo (n=89)	Children aged between 6-12, diagnosis of ADHD according to DSM-IV criteria (n=209)	ADHD symptoms (ADHD Rating Scale) at 16 weeks	55% previous stimulant use. 48% combined subtype, 49.8% inattentive subtype. Baseline scores of ADHD-RS show the majority of the population had severe ADHD.
Wilens 2015 ⁶⁹⁴	Intervention: Extended release guanfacine, max dose 4-7mg depending on weight (n=157) Comparison: Placebo (n=155)	Children aged 13-17 who met DSM-IV criteria for ADHD (n=312)	ADHD symptoms (ADHD Rating Scale) at 13 weeks Academic achievement at 13 weeks Discontinuation due to adverse events at 13 weeks	Around 75% of the population had previously used stimulant medication Baseline scores of CGI-S show the majority of the population

Study	Intervention and comparison	Population	Outcomes	Comments
				had moderate ADHD. 68% combined subtype, 29% inattentive subtype, 3% hyperactive subtype.
Wolraich 2001 ⁷⁰¹	Intervention: IR-Methylphenidate 18-54mg/day(n=94) Intervention 2: OROS-MPH 18-54mg/day (n=95) Comparison: placebo (n=89)	Children and adolescents 6-12 meeting DSM-IV-TR ADHD criteria (n=278)	ADHD symptoms (IOWA Conners and SNAP-IV) at 4 weeks Clinical global impressions – improvement at 4 weeks Discontinuation due to adverse events at 4 weeks	73.4% combined, 19.5% inattentive and 7.1% hyperactive/impulsive 20.2%received no stimulant therapy, 67.7% methylphenidate , 5.7% other medication, 6.4% hadn't received any medication in the previous 4 weeks Severity not stated
Zarinara 2010 ⁷¹¹	Intervention: Venlafaxine 50mg if <30kg, 75mg if >30kg (n=19) Comparison: Methylphenidate 20mg if <30kg, 30mg if >30kg (n=19)	Children aged 6-13 diagnosed with ADHD as per the DSM-IV-TR criteria. (n=38)	ADHD symptoms (ADHD Rating Scale) at 6 weeks	Unclear line of treatment All participants combined subtype. Baseline ADHD-RS-IV scores were ~ 30 (teacher)

1 See appendix D for full evidence tables.

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3 1.1.3.5 Included studies (adults)

4 39 RCTs were included in the review^{8, 11, 12, 16, 21, 34, 50, 84, 90, 91, 110, 117, 140, 162, 216, 281, 286, 287, 305, 385}
5 ,392, 400, 445, 448, 493, 521, 523, 526, 532, 590, 592, 607, 619, 620, 624, 665, 666, 688, 710 that evaluated the effectiveness
6 of pharmacological treatments in adults these are summarised in Table 4 below. The
7 following comparisons were included in this review:

- 8 • Eight RCTs compared immediate release methylphenidate versus placebo^{21, 110, 385, 392}
9 ,590, 592, 624, 665

- twelve RCTs compared controlled release methylphenidate versus placebo^{21,90,91,117,140,162,281,286,445,523,532,592}
- three RCTs compared dexamphetamine versus placebo^{493,619,620}
- three RCTs compared lisdexamfetamine versus placebo^{8,11,84}
- ten RCTs compared atomoxetine versus placebo^{12,16,216,287,400,448,607,666,688,710}
- one RCT compared guanfacine versus placebo⁶²⁰
- one RCT compared guanfacine versus dexamphetamine⁶²⁰
- one RCT compared reboxetine versus placebo⁵²⁶
- one RCT compared venlafaxine versus placebo³⁴
- two RCTs compared bupropion versus placebo^{305,392}
- one RCT compared bupropion versus methylphenidate³⁹²
- two RCTs compared modafinil versus placebo^{50,619}
- one RCT compared modafinil versus dexamphetamine⁶¹⁹
- one RCT compared atomoxetine and buspirone versus placebo⁶⁰⁷

Evidence from these studies is summarised in the clinical evidence summary below (Table 37, Table 38, Table 39, Table 40, Table 41, Table 42, Table 43, Table 44, Table 45, Table 46 Table 47, Table 48, Table 49, Table 50).

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.

Table 4: Summary of studies included in the review for adults

Study	Intervention and comparison	Population	Outcomes	Comments
Adler 2008 ¹¹ (Mattingly 2013 ⁴³⁵ , Adler 2009 ¹⁰ , Kollins 2011 ³⁸⁰)	Interventions: Lisdexamfetamine dimesylate 30mg/d (n=119), lisdexamfetamine dimesylate 50mg/d (n=117), lisdexamfetamine 70mg/d (n=122) Comparison: Placebo (n=62)	Adults aged 18-55 years diagnosed with ADHD according to DSM-IV criteria. (n=420)	Clinical Global Impressions - Improvement scale at 4 weeks Discontinuation due to adverse events at 4 weeks	Unclear line of treatment. All subjects had moderate to severe ADHD as rated by a clinician on ADHD-RS (scores 28 or above).
Adler 2009 ¹²	Intervention: Atomoxetine 80mg/d (n=224) Comparison: Placebo (n=218)	Adults aged 18-65 who met DSM-IV criteria for ADHD and social anxiety disorder. (n=442)	Quality of life at 16 weeks ADHD symptoms (Conners Adult ADHD Rating scale) at 16 weeks CGI-I at 16 weeks Discontinuation due to adverse events at 16 weeks	Unclear line of treatment. 86.9% generalized social anxiety disorder, 23.3% also had generalised anxiety disorder. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Adler 2009 ¹⁶ (Brown 2011 ¹²¹)	Intervention: Atomoxetine (mean dose 84.5mg/day) (n=94)	Adults aged 18 to 54 years who met the DSM-IV criteria for ADHD (n=206)	Quality of life at 6 months ADHD symptoms (Adult ADHD Self Report; Adult	72% combined subtype Unclear line of treatment; exclusion

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison: Placebo (n=112)		ADHD Investigator Symptom Rating Scale; Conners Adult ADHD Rating Scale) at 6 months Discontinuation due to adverse events (6 months)	criteria: failure to respond to an adequate trial of ADHD stimulant medication, bupropion or other non-stimulant medications.
Adler 2009 ²¹	Intervention: Methylphenidate 36-108mg/day (mean dose 67.7mg/day) (n=113) Comparison: Placebo (n=116)	Adults aged 18 to 65 years who met the DSM-IV criteria for ADHD (n=229)	ADHD symptoms (Adult ADHD Investigator Symptom Report Scale) at 7 weeks Discontinuation due to adverse events at 7 weeks	Severity: AISRS score of 24 or higher Unclear line of treatment; known non-responders were excluded from the study 80% combined subtype
Adler 2013 ⁸ (Adler 2013 ⁹	Intervention: Lisdexamfetamine dimesylate (30-70mg/day) (n=80) Comparison: Placebo (n=81)	Adults aged 18 to 55 years who met the DSM-IV criteria for ADHD (n=161)	ADHD symptoms (ADHD Rating Scale) at 10 weeks Quality of life at 10 weeks Discontinuation due to adverse events at 10 weeks	81.11% combined, 18.24% inattentive, 0.63% hyperactive-impulsive Severity: baseline score of 39.9 on ADHD-RS Line of treatment unclear
Amiri 2012 ³⁴	Intervention: Venlafaxine 75mg TDS (n=22) Comparison: Placebo (n=22)	Adults aged 18-45 years diagnosed with ADHD according to DSM-IV criteria. (n=44)	ADHD symptoms (Conners Adult ADHD Rating scale) at 6 weeks Serious adverse events at 6 weeks Discontinuation due to adverse events at 6 weeks	All participants were drug naïve. The participants were parents or siblings of children diagnosed to have ADHD.
Arnold 2014 ⁵⁰	Intervention 1: Modafinil 255mg/day (n = 73) Intervention 2: Modafinil 340mg/day (n = 73) Intervention 3: Modafinil 425mg/day (n=74) Intervention 4: Modafinil	Adults aged 18 and over diagnosed with ADHD according to DSM-IV criteria. (n = 338)	Quality of life at 9 weeks ADHD symptoms (Adult ADHD Self Report Scores) at 9 weeks Behavioural outcomes at 9 weeks Discontinuation due to adverse events at 9 weeks	37% of the population had received ADHD medication within the last 5 years. Baseline CGI-S scores show the majority of the population had moderate ADHD.

Study	Intervention and comparison	Population	Outcomes	Comments
	510mg/day (n=44) Comparison: Placebo (n = 74)			
Biederman 2006 ⁹⁰	Intervention: Methylphenidate CR, maximum dose of 1.3mg/kg (n=72) Comparison: Placebo (n=77)	Adults aged 19-60 years with ADHD according to DSM-IV (n=149)	Discontinuation due to adverse events at 6 weeks	Unclear line of treatment. Baseline CGI-S scores show the majority of the population had moderate ADHD.
Biederman 2010 ⁹¹	Intervention: OROS methylphenidate, max dose 1.3 mg/kg (n = 112) Comparison: Placebo (n=115)	Adults aged 19-60 years with ADHD according to DSM-IV (n=227)	ADHD symptoms (Adult ADHD Investigator Symptom Report Scale) at 6 weeks Discontinuation due to adverse events at 6 weeks	Unclear line of treatment
Biederman 2012 ⁸⁵	Intervention: Lisdexamfetamine , max dose 70mg/day (n=35) Comparison: Placebo (n=34)	Adults aged 18-26 years with ADHD according to DSM-IV (n=69)	ADHD symptoms (ADHD Rating scale) at 6 weeks Behavioural outcomes at 6 weeks Discontinuation due to adverse events at 6 weeks	Unclear line of treatment.
Bouffard 2003 ¹¹⁰	Intervention: IR methylphenidate, max dose 15 mg TDS Comparison: Placebo Crossover trial: (n=38)	Adults aged 17-51 years with ADHD according to DSM-IV	ADHD symptoms (Conners Adult ADHD Rating scale) at 4 weeks Behavioural outcomes at 4 weeks	Unclear line of treatment. All subjects scored 1.5 or more on at least 1 ADHD self-report questionnaire (either Conners' Adult ADHD Rating Scale or the Adult ADHD Problem Behaviours scale)
Bron 2014 ¹¹⁷	Intervention: OROS methylphenidate 72mg per day Comparison: Placebo Crossover trial: (n=27)	Adults aged 18-55 years with ADHD diagnosed by DSM-IV	Discontinuation due to adverse events at 6 weeks	All participants were drug naïve, and were initiated in an open label methylphenidate phase, followed by the double blind phase. All participants had combined subtype of ADHD. Baseline scores of ADHD-RS show the majority of

Study	Intervention and comparison	Population	Outcomes	Comments
				the population had moderate ADHD.
Casas 2013 ¹⁴⁰ (Kooij 2013 ³⁸⁶)	Intervention: OROS Methylphenidate 54-72mg/day (n=182) Comparison: Placebo (n=97)	Adults aged 18-65 years who met the DSM-IV criteria for ADHD (n=279)	ADHD symptoms (Conners self-reported and investigator reported scales) at 13 weeks Discontinuation due to adverse events at 13 weeks	70% combined subtype; 26% inattentive; 4% hyperactive-impulsive CAARS-O:SV score of 36 Unclear line of treatment; known non-responders to methylphenidate were excluded.
Chronis-tuscano 2008 ¹⁶²	Intervention: Methylphenidate, max dose 90 mg (n=9) Comparison: Placebo (n=11)	Adults aged 18 and over with ADHD diagnosed by DSM-IV (n=20)	ADHD symptoms (Conners Adult ADHD Rating Scale) at 2 weeks	Unclear line of treatment. Participants included mothers, 56.5% of the study population comprising mothers were of the combined subtype of ADHD, 34.8% of the inattentive subtype and 8.7% of the hyperactive/impulsive subtype. Baseline scores of CGI-S show the majority of the population had mild ADHD.
Durrell 2013 ²¹⁶ (Adler 2014 ⁷)	Intervention: Atomoxetine, 80-100mg/day. Mean dose 87.1mg/day (n=220) Comparison: Placebo (n=225)	Adults aged 18-30 years that met DSM-IV criteria for ADHD (n=445)	Quality of life at 12 weeks ADHD symptoms (Conners Adult ADHD Rating Scale) at 12 weeks Behavioural outcomes at 12 weeks Discontinuation due to adverse events at 12 weeks	64% of subjects were drug naïve. Baseline scores of CGI-S show the majority of the population had moderate ADHD. 78% had combined subtype, 21.6% had the inattentive subtype and 0.45% had the hyperactive/impulsive subtype.
Ginsberg 2012 ²⁸¹	Intervention: Methylphenidate OROS 72mg/d (n=15) Comparison: Placebo (n=15)	Adult male prison inmates aged 21-61 years with ADHD according to DSM-IV criteria. (n=30)	ADHD symptoms (Conners Adult ADHD Rating Scale) at 5 weeks Behavioural outcomes at 5 weeks	14% had previously received pharmacological treatment. 93% were of the combined subtype of ADHD, 7% were

Study	Intervention and comparison	Population	Outcomes	Comments
				<p>predominantly inattentive subtype. 23.3% of the study population reported lifetime psychiatry co-morbidity of autism-spectrum disorder, 73% reported mood and anxiety disorder, 100% reported duct disorder, 97% had antisocial personality disorder and 10% demonstrated psychotherapy as a co-morbidity. All participants had a lifetime substance use disorder. Baseline scores on CAARS-O:SV, ASRS, CGI-S and GAF show participants had severe ADHD</p>
Goodman 2016 ²⁸⁶	<p>Intervention: Methylphenidate OROS 72mg/d (n=178)</p> <p>Comparison: Placebo (n=179)</p>	Adult male prison inmates aged 18-65 years with ADHD according to DSM-IV criteria. (n=357)	<p>ADHD symptoms (Adult ADHD symptom rating scale) at 6 weeks</p> <p>Discontinuation due to adverse events at 6 weeks</p>	<p>Unclear line of treatment</p> <p>81% were of the combined subtype of ADHD, 2% were predominantly inattentive subtype. 17% of the study population reported lifetime psychiatry co-morbidity of autism-spectrum disorder, 73% reported mood and anxiety disorder, 100% reported duct disorder, 97% had antisocial personality disorder and 10% demonstrated psychotherapy as a co-morbidity. All participants had a lifetime substance use disorder. Baseline scores on CAARS-O:SV, ASRS, CGI-S and GAF show participants had severe ADHD</p>
Goto 2013	Intervention:	Adults aged 18	ADHD symptoms	22% had prior

Study	Intervention and comparison	Population	Outcomes	Comments
²⁸⁷	Atomoxetine (n=195) Placebo (n=196)	and over who met DSM-IV criteria for ADHD (n=391)	(Conners Adult ADHD Rating Scale) at 10 weeks Quality of life at 10 weeks Discontinuation due to adverse events at 10 weeks	stimulant exposure All participants were required to have a CGI-S score of 4 or more.
Hamedi 2014 ³⁰⁵	Intervention: Bupropion 150mg/day (n=21) Comparison: placebo (n=21)	Adults aged 20 to 60 years who met DSM-IV criteria for ADHD (n=42)	ADHD symptoms at 6 weeks	Unclear subtype and line of treatment.
Kooij 2004 ³⁸⁵	Intervention 1: Methylphenidate IR, titrated up to 1mg/kg/day Comparison: Placebo Crossover trial: (n=45)	Adults aged 20-56 who met DSM-IV criteria for ADHD	ADHD symptoms (DSM-IV) at 3 weeks Discontinuation due to adverse events at 3 weeks	Stimulant naïve population. All subtypes were included. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Kuperman 2001 ³⁹²	Intervention 1: Bupropion SR, maximum dose 300mg/day (n=11) Intervention 2: Methylphenidate IR, max dose 0.9mg/kg/day (n=8) Comparison: Placebo (n=11)	Adults aged 18-60 years who met DSM-IV criteria for ADHD (n=30)	ADHD symptoms (ADHD Rating Scale) at 7 weeks Discontinuation due to adverse events at 7 weeks	Unclear line of treatment. Baseline scores of CGI-S show the majority of the population had mild ADHD.
Lee 2014 ⁴⁰⁰	Intervention: Atomoxetine, maximum dose 120mg daily (n=37) Comparison: Placebo (n=37)	Adults aged 18 and over who met DSM-IV criteria for ADHD (n=74)	Quality of life at 10 weeks ADHD symptoms (Conners Adult ADHD Rating Scale) at 10 weeks Discontinuation due to adverse events at 10 weeks	19.2% had previous treatment with stimulants. All subtypes were included: Inattentive (39.7%). Hyperactive/impulsive (4.1%), Combined (56.2%). All patients had a score of 2 or more on 6 or more items of either the inattentive or hyperactive/impulsive subscale scores,

Study	Intervention and comparison	Population	Outcomes	Comments
				CGI-ADHD-S score of 4 or more at baseline. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Medori 2008 ⁴⁴⁵	Intervention: Methylphenidate 18-72mg/day (n=305) Comparison: Placebo (n=96)	Adults aged 18 to 65 years who met DSM-IV criteria for ADHD (N=401)	ADHD symptoms (CAARS self-report) at 5 weeks Discontinuation due to adverse events at 5 weeks	70.8% combined subtype; 24.2% inattentive subtype; 4% hyperactive-impulsive subtype (1% unspecified) Severity: Conners Adult ADHD score of >24. Unclear line of treatment: non-responders to methylphenidate were excluded
Michelson 2003 ⁴⁴⁸	Intervention: Atomoxetine 80-120mg/d (n=270) Comparison: Placebo (n=266)	Adults aged 18 and over who met DSM-IV criteria for ADHD (n=536)	ADHD symptoms (Conners Adult ADHD rating scale) at 8 weeks Discontinuation due to adverse events at 8 weeks	66.4% combined, 31% inattentive, 2.6% hyperactive/impulsive Unclear line of treatment; patients responding to initial placebo trial were excluded Baseline scores of CGI-S score show the majority of the population had moderate ADHD
Paterson 1999 ⁴⁹³	Intervention: Dexamphetamine, up to six tablets per day (n=24) Comparison: Placebo (n=21)	Adults aged 19-57 who met DSM-IV criteria for ADHD (n=45)	Clinical Global Impressions - Improvement at 6 weeks	Unclear line of treatment. All subtypes were included. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Retz 2012 ⁵²³	Intervention: Methylphenidate CR, maximum daily dose 1mg/kg (n=84)	Adults aged 18 and over who met DSM-IV criteria for ADHD (n=162)	ADHD symptoms (Wender-Reimherr Adult Attention Deficit Disorder Scale) at 8 weeks	Unclear line of treatment. Baseline scores of CGI-S show the majority of the population had

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison: Placebo (n=78)		Clinical Global Impressions - Improvement at 8 weeks Discontinuation due to adverse events at 8 weeks	moderate ADHD.
Reimherr 2007 ⁵²¹ (Robison 2010 ⁵²⁹)	Intervention: Methylphenidate 18-90mg/day Comparison: placebo Crossover trial (n=47)	Adults aged 18 to 65 years who met the DSM-IV criteria for ADHD	ADHD symptoms (ADHD-RS) at 4 weeks Clinical global impressions (improvement) at 4 weeks Emotional dysregulation at 4 weeks	Line of treatment not specified Subtype not specified Baseline ADHD-RS scores of 36.2
Riahi 2010 ⁵²⁶	Intervention: Reboxetine, 4 mg BD (n=23) Comparison: Placebo (n=17)	Adults aged 18 and over who met DSM-IV criteria for ADHD (n=40)	ADHD symptoms (Conners Adult ADHD Rating Scale) at 6 weeks Behavioural outcomes at 6 weeks Discontinuation due to adverse events at 6 weeks	Unclear line of treatment.
Rosler 2009 ⁵³² (Rosler 2010 ⁵³⁴)	Intervention: Methylphenidate CR, maximum dose 60mg/day (n=241) Comparison: Placebo (n=118)	Adults age 18 and over who met DSM-IV criteria for ADHD (n=359)	Emotional dysregulation at 24 weeks	38% of the population had previous treatment for ADHD.
Spencer 1995 ⁵⁹²	Intervention: Methylphenidate average dose 0.92mg/kg per day Comparison: placebo Crossover trial (n=25)	Adults aged 18 to 60 years who met the DSM-III criteria for ADHD	Clinical global impressions – improvement at 3 weeks	Unclear line of treatment Unclear subtype Unclear severity
Spencer 2005 ⁵⁹⁰ (Biederman 2006 ⁹⁰)	Intervention: Methylphenidate IR, maximum dose of 1.3mg/kg (n=104) Comparison: Placebo (n=42)	Adults aged 19-60 years with ADHD according to DSM-IV (n=146)	ADHD symptoms (Adult ADHD Investigator Symptom Report Scale) at 6 weeks	Unclear line of treatment. Subjects met full DSM-IV-R criteria (at least six of nine symptoms) for inattentive or hyperactive/impulsive subtypes (or both)

Study	Intervention and comparison	Population	Outcomes	Comments
				by age 7 and within the past month.
Sutherland 2012 ⁶⁰⁷	Intervention: Atomoxetine 80-100mg/d (n=97) Intervention 2: Combination atomoxetine (80mg/d) and bupirone (40mg/d) (n=97) Placebo (n=47)	Adults aged 18-60 years with ADHD according to DSM-IV-TR criteria and AISRS (n=241)	ADHD symptoms (Adult ADHD Investigator Symptom Report Scale) at 8 weeks	Unclear line of treatment. All subjects had to have a score of 24 or more on the AISRS scale, Mean scores AISRS = 36
Taylor 2000 ⁶¹⁹	Interventions: Dexamphetamine, max dose 40 mg/day Modafinil, max dose 400 mg/day Comparison: Placebo Crossover trial: (n=22)	Adults aged 18-59 years with ADHD according to DSM-IV	ADHD symptoms (DSM-IV Rating scale) at 2 weeks	Unclear line of treatment. Subjects had to meet full DSM-IV criteria for the disorder by the age of 7 years as well as currently. 11 subjects were of the inattentive subtype, 9 were of the combined subtype and 2 were of the hyperactive subtype
Taylor 2001 ⁶²⁰	Interventions: Dexamphetamine, max dose 20 mg/day Guanfacine, max dose 2 mg/day Comparison: Placebo Crossover trial: (n=17)	Adults who met DSM-IV criteria for ADHD	ADHD symptoms (DSM-IV Rating scale) at 2 weeks	Unclear line of treatment. Subjects had to meet full DSM-IV criteria for the disorder by the age of 7 years as well as currently.
Tenenbaum 2002 ⁶²⁴	Intervention: Methylphenidate IR, gradually titrated up to 15mg TDS Comparison: Placebo Crossover trial: (n=24)	Adults aged 24-53 years with ADHD according to DSM-IV-TR criteria	ADHD symptoms (Barkleys ADHD Rating Scale) at 3 weeks	Unclear line of treatment. All subjects were diagnosed with the combined subtype of ADHD.
Wender 1985 ⁶⁶⁵	Intervention: Methylphenidate IR Comparison:	Adults who met DSM III criteria for ADHD	Behavioural outcomes at 2 weeks	Unclear line of treatment. All subjects had ADHD, residual type

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo			
	Crossover trial: (n=37)			
Wernicke 2004 ⁶⁶⁶	Intervention: Atomoxetine 2mg/kg/d (n=102) Comparison: Placebo (n=92)	Adults who met DSM-IV criteria for ADHD (n=284; 90 not relevant to this review)	ADHD symptoms (Conners Adult ADHD Rating Scale) at 9 weeks	Line of treatment not stated
Wilens 2008 ⁶⁸⁸	Intervention: Atomoxetine 25- 100mg/d (n=72) Comparison: Placebo (n=75)	Adults over the age of 18 who met DSM-IV criteria for ADHD and had an ADHD symptoms score >20 on the AISRS. (n=147)	Clinical Global Impressions scale at 13 weeks ADHD symptoms (Adult ADHD Investigator Symptom Report Scale) at 13 weeks Behavioural outcomes at 13 weeks Discontinued due to adverse events at 13 weeks	Unclear line of treatment. Subjects also met DSM-IV-TR criteria for alcohol use disorders (abuse or dependence). AISRS baseline = ~40.3, ASRS baseline = 50, CGI-S baseline = 4.8. Baseline scores of CGI-S show the majority of the population had moderate ADHD.
Young 2011 ⁷¹⁰ (Wietecha 2012 ⁶⁷⁰)	Intervention: Atomoxetine 60- 100mg/d (n=268) Comparison: Placebo (n=234)	Adults over the age of 18, who met DSM-IV-TR criteria for adult ADHD, had a historical diagnosis during childhood and a CGI-ADHD-S score of 4+. (n=502)	ADHD symptoms (Conners Adult ADHD Rating Scale) at 24 weeks Discontinuation due to adverse events at 24 weeks	84% of the subjects were stimulant naïve. 68.7% of the study population were of the combined subtype of ADHD, 31.1% of inattentive subtype, 0.2% of the hyperactive/ impulsive subtype. No co-morbid conditions reported. Participants randomised to the intervention arm were initiated to treatment during an assessment stage prior to the trial. Participants who were unable to tolerate the drug were excluded from the trial. Baseline scores of CGI-S show the majority of the population had moderate ADHD.

1 See appendix D for full evidence tables.

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1.1.3.6 Quality assessment of clinical studies included in the evidence review (children under the age of 5)

Table 5: Clinical evidence summary: Methylphenidate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate versus placebo (95% CI)
ADHD total symptoms (SNAP-IV total scores, parent-teacher rated, ≤ 1)	114 (1 study) 4 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 2.14 (0.92 to 4.96)	115 per 1000	131 more per 1000 (from 9 fewer to 454 more)
ADHD total symptoms parent rated (CPRS DSM-IV ADHD subscale); 0-54, lower values are beneficial	14 (1 study) 4 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms score in the control groups was 30.75	The mean ADHD symptoms score in the intervention groups was 8.92 lower (17.97 lower to 0.13 higher)
Behavioural symptoms (CGAS); 0-100; lower values are beneficial	14 (1 study) 4 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean CGAS score in the control groups was 54.33	The mean CGAS score in the intervention groups was 4.83 lower (11.13 lower to 1.47 higher)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 6: Clinical evidence summary: Risperidone versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus methylphenidate (95% CI)
ADHD symptoms (ADHD-RS total scores) Parent rated; 0-54; lower values are beneficial	33 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS total score in the control groups was 15.3	The mean ADHD-RS total score in the intervention groups was 1.34 higher (4.21 lower to 6.89 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus methylphenidate (95% CI)
ADHD symptoms (ADHD-RS inattentive subscale scores) parent rated; 0-27; lower values are beneficial	33 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS inattentive subscale in the control groups was 6.84	The mean ADHD-RS inattentive subscale in the intervention groups was 0.74 higher (2.04 lower to 3.51 higher)
ADHD symptoms (ADHD-RS hyperactivity subscale) parent rated; 0-27; lower values are beneficial	33 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS hyperactive subscale in the control groups was 8.69	The mean ADHD-RS hyperactive subscale in the intervention groups was 0.31 higher (3.16 lower to 3.8 higher)
Discontinuation due to adverse events	38 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 0.6 (0.11 to 3.19)	167 per 1000	67 fewer per 1000 (from 148 fewer to 365 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 7: Clinical evidence summary: Risperidone and methylphenidate versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard Treatment (pre-schoolers)	Risk difference with Risperidone (95% CI)
ADHD total symptoms (parent rated CPRS total scores, 0-81, low scores are beneficial)	42 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms parent rated score in the control groups was 33.85	The mean parent rated ADHD symptoms score in the intervention groups was 3.33 lower (12.72 lower to 6.06 higher)
ADHD Inattention symptoms (parent rated; CPRS inattention subscale; 0-	42 (1 study)	VERY LOW ^{1,2} due to risk of		The mean ADHD symptoms parent	The mean parent rated ADHD inattention symptoms score in the intervention groups

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard Treatment (pre-schoolers)	Risk difference with Risperidone (95% CI)
18, low scores are beneficial)	6 weeks	bias, imprecision		rated score in the control groups was 6.67	was 0 higher (2.35 lower to 2.35 higher)
ADHD hyperactivity symptoms (parent rated; CPRS hyperactivity subscale; 0-18, low scores are beneficial)	42 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms parent rated score in the control groups was 7.14	The mean parent rated ADHD hyperactivity score in the intervention groups was 0.38 higher (1.95 lower to 2.71 higher)
CGI-I score of 1 or 2 (high scores are beneficial)	42 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 1.23 (0.82 to 1.86)	619 per 1000	142 more per 1000 (from 111 fewer to 532 more)
Behaviour outcomes (parent rated CPRS oppositional defiant disorder subscale; 0-18, low scores are beneficial)	42 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms parent rated score in the control groups was 8.76	The mean behaviour outcome score in the intervention groups was 1.52 lower (3.82 lower to 0.78 higher)
Discontinued due to adverse events	42 (1 study) 6 weeks	LOW ¹ due to risk of bias	OR 9.17 (1.45 to 58.07)		240 more per 1000 (from 50 to 530 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

1 **1.1.3.7 Quality assessment of clinical studies included in the evidence review (children aged 5 to 18 years)**

2 **Table 8: Clinical evidence summary: Immediate release methylphenidate versus placebo**

Outcomes	No of	Quality of	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Immediate release methylphenidate versus placebo (95% CI)
ADHD total symptoms parent rated (Abbreviated parent rating scale and Conners ADHD index; lower values are beneficial)	62 (2 studies) 4-7 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms parent rated score in the control groups was 77.2	The mean parent rated ADHD symptoms score in the intervention groups was 0.53 standard deviations lower (0.91 to 0.16 lower)
ADHD total symptoms parent rated (ASQ-P; 0-20; low values are beneficial; change scores reported)	128 (2 studies) 16 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean parent rated ADHD symptoms score in the intervention groups was 3.71 lower (6.71 lower to 0.7 lower)
ADHD total symptoms parent rated, (Conners ADHD index; PT; 0-30; low values are beneficial; final values reported)	122 (1 study) 16 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms parent rated score in the control groups was 22.4	The mean parent rated ADHD symptom score in the intervention groups was 3.3 lower (3.75 to 2.85 lower)
ADHD total symptoms teacher rated (Conners ADHD index and abbreviated parent rating scale; lower values are beneficial; final values reported; crossover trials)	62 (2 studies) 4-7 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms parent rated score in the control groups was 58.5	The mean parent rated ADHD symptoms score in the intervention groups was 0.94 standard deviations lower (1.33 to 0.55 lower)
ADHD total symptoms teacher rated (ASQ-T; 0-20; low values are beneficial; change scores reported)	128 (2 studies) 16 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms teacher rated score in the control groups was -3.2	The mean parent rated ADHD symptoms score in the intervention groups was 2.93 lower (5.51 to 0.36 lower)
ADHD total symptoms teacher rated, (Conners ADHD index; 0-30; lower values are beneficial; final values reported)	122 (1 study) 16 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms parent rated score in the control groups was 18.6	The mean parent rated ADHD symptom score in the intervention groups was 4.1 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Immediate release methylphenidate versus placebo (95% CI)
values reported)					(4.54 lower to 3.66 lower)
ADHD hyperactivity symptoms parent rated; (SNAP-IV and parent symptom questionnaire hyperactivity subscales, lower values are beneficial)	221 (2 studies) 4-8 weeks	MODERATE ¹ due to risk of bias		The mean parent rated ADHD hyperactivity symptom score in the control groups was 1.83	The mean parent rated ADHD hyperactivity symptom score in the intervention groups was 0.92 standard deviations lower (1.20 to 0.64 lower)
ADHD hyperactivity symptoms parent rated; (Conners Parent ADHD Index Hyperactivity subscale), 0-15, lower values are beneficial	122 (1 study) 16 weeks	LOW ^{1,3} due to risk of bias, imprecision		The mean parent rated ADHD hyperactivity symptom score in the control groups was 9.2	The mean parent rated ADHD hyperactivity symptom score in the intervention groups was 1.5 lower (3.44 lower to 0.44 higher)
ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale; 0-3, PT; lower values are beneficial)	183 (1 study) 4 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD hyperactivity symptom score in the control groups was 1.57	The mean ADHD hyperactivity symptom score in the intervention groups was 0.31 lower (0.55 to 0.07 lower)
ADHD hyperactivity symptoms teacher rated (Conners Teacher ADHD Index (Hyperactivity; 0-15, lower values are beneficial)	122 (1 study) 16 weeks	LOW ^{1,3} due to risk of bias, imprecision		The mean ADHD hyperactivity score in the control groups was 9	The mean ADHD hyperactivity score in the intervention groups was 2.6 lower (4.68 to 0.52 lower)
ADHD inattention symptoms parent rated; (SNAP-IV inattention subscale; 0-3; lower values are beneficial)	183 (1 study) 4 weeks	MODERATE ¹ due to risk of bias		The mean SNAP-IV inattention subscale score in the control groups was 2	The mean SNAP-IV inattention subscale score in the intervention groups was 0.61 lower (from 0.83 lower to 0.39 lower)
ADHD inattention	183	MODERATE ¹		The mean SNAP-IV inattention	The mean SNAP-IV inattention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Immediate release methylphenidate versus placebo (95% CI)
symptoms teacher rated; (SNAP-IV inattention subscale; 0-3; lower values are beneficial)	(1 study) 4 weeks	due to risk of bias		subscale score in the control groups was 1.97	subscale score in the intervention groups was 0.71 lower (0.94 to 0.48 lower)
CGI-I score of 1 or 2 (much improved or very much improved)	532 (3 studies) 3 to 9 weeks	MODERATE ¹ due to risk of bias	RR 1.85 (1.56 to 2.19)	373 per 1000	317 more per 1000 (from 209 more to 443 more)
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial	126 (2 studies) 16 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean children's global assessment scale in the intervention groups 9.15 higher (4.21 to 14.08 higher)
Discontinued due to adverse events	352 (2 studies) 3 weeks	LOW ¹ due to imprecision	OR 7.3 (0.76 to 70.45)	0 events in control arm	1 more per 1000 (from 1 fewer to 3 more)
Discontinued due to adverse events	181 (2 studies) 16 weeks	LOW ³ due to imprecision	OR 7.87 (1.55 to 39.86)	0 events in control arm	2 more per 1000 (from 20 fewer to 20 more)
Serious adverse events	144 (1 study) 3 weeks	MODERATE ¹ due to risk of bias	RD 0 (-0.01 to 0.01)	0 events in control arm	0 events in both arms

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Control group risk not reported

Table 9: Clinical evidence summary: OROS Methylphenidate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with OROS Methylphenidate versus placebo (95% CI)
Quality of life (Child Health Questionnaire); 0-100, higher values are beneficial)	102 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean child health questionnaire score in the control groups was 1.4	The mean child health questionnaire score in the intervention groups was 8.4 higher (3.14 to 13.66 higher)
ADHD total symptoms parent rated (Conners Parent Rating Scale; 0-54, lower values are beneficial, change scores)	109 (1 study) 8 weeks	MODERATE ¹ due to risk of bias		The mean parent rated ADHD symptoms score in the control groups was -3.9	The mean parent rated ADHD symptoms score in the intervention groups was 9.6 lower (13.67 to 5.53 lower)
ADHD total symptoms parent rated (SNAP-IV, 0-3, lower values are beneficial; final values)	102 (1 study) 6 weeks	MODERATE ¹ due to risk of bias		The mean parent rated ADHD symptoms score in the control groups was 1.4	The mean parent rated ADHD symptoms score in the intervention groups was 0.41 lower (0.79 to 0.03 lower)
ADHD total symptoms teacher rated (SNAP-IV; 0-3, lower values are beneficial)	38 (1 study) 8 weeks	MODERATE ¹ due to risk of bias		The mean teacher rated ADHD symptoms score in the control groups was 1.5	The mean teacher rated SNAP-IV score in the intervention group was 0.37 lower (0.69 to 0.05 lower)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial	116 (1 study) 7 weeks	MODERATE ¹ due to risk of bias		The mean investigator rated ADHD symptom score was -5.7	The mean investigator rated ADHD symptom score in the intervention groups was 13 lower (16.05 to 9.95 lower)
ADHD inattention symptoms investigator rated (ADHD-RS Inattentive	109 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias,		The mean ADHD-RS inattentive subscale score in the control groups was -5.2	The mean ADHD-RS inattentive subscale score 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 Control	Risk difference with OROS Methylphenidate versus placebo (95% CI)
subscale); 0-27, lower values are beneficial		imprecision			5.8 lower (9 to 2.6 lower)
ADHD inattention symptoms teacher rated (SNAP-IV Inattentive subscale); 0-3 Lower values are beneficial	221 (2 studies) 4 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean teacher SNAP-IV inattentive subscale score in the control groups was 1.84	The mean teacher rated SNAP-IV inattentive subscale score in the intervention groups was 0.54 lower (0.74 to 0.38 lower)
ADHD inattention symptoms parent rated (SNAP-IV Inattentive subscale); 0-3, lower values are beneficial, change scores reported	221 (2 studies) 4 weeks	MODERATE ¹ due to risk of bias		The mean parent rated SNAP-IV inattentive subscale score in the control groups was 1.7	The mean parent rated SNAP-IV inattentive subscale score in the intervention groups was 0.57 lower (0.74 to 0.34 lower)
ADHD hyperactivity symptoms investigator rated (ADHD-RS Hyperactive subscale); 0-27, Lower values are beneficial, change scores reported	109 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS hyperactive subscale score in the control groups was -3.8	The mean ADHD-RS hyperactive subscale score in the intervention groups was 4.9 lower (7.47 to 2.33 lower)
ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale); 0-3 Lower values are beneficial, change scores reported	221 (2 studies) 4 weeks	MODERATE ¹ due to risk of bias		The mean teacher SNAP-IV hyperactivity subscale score in the control groups was 1.5	The mean teacher rated SNAP-IV hyperactivity subscale score in the intervention groups was 0.67 lower (0.87 to 0.47 lower)
ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale); 0-3 Lower values are beneficial,	221 (2 studies) 4 weeks	MODERATE ¹ due to risk of bias		The mean parent rated SNAP-IV hyperactivity subscale score in the control groups was 1.4	The mean parent rated SNAP-IV hyperactivity subscale score in the intervention groups was 0.63 lower (0.83 to 0.43 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with OROS Methylphenidate versus placebo (95% CI)
change scores reported					
Clinical global impressions – improvement (score of 1 or 2)	396 (2 studies) 4-7 weeks	MODERATE ¹ due to risk of bias	RR 3.5 (2.42 to 5.06)	144 per 1000	359 more per 1000 (from 207 more to 593 more)
Behavioural outcomes (WFIRS-P total; 0-3, lower values are beneficial)	222 (1 study) 7 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean children’s global assessment scale in the intervention groups was 0.77 standard deviations lower (1.23 lower to 0.31 lower)
Academic achievement (CHIP-CE academic achievement subscale; 0-100; high scores are beneficial)	221 (1 study) 7 weeks	LOW ¹ due to risk of bias		The mean CHIP-CE academic achievement subscale score in the control group was 29.3	The mean CHIP-CE academic achievement subscale score in the intervention groups was 8.4 higher (5.59 higher to 11.21 higher)
Discontinuation due to adverse events	582 (3 studies) 4-7 weeks	LOW ² due to imprecision	RR 0.81 (0.25 to 2.62)	21 per 1000	4 fewer per 1000 (from 16 fewer to 34 more)
<p>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 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

Table 10: Clinical evidence summary: IR methylphenidate versus OROS methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IR Methylphenidate versus OROS Methylphenidate (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with IR Methylphenidate versus OROS Methylphenidate (95% CI)
ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale; 0-3; lower values are beneficial)	194 (1 study) 4 weeks	MODERATE ¹ due to risk of bias		The mean SNAP-IV inattention subscale score in the control groups was 1.34	The mean SNAP-IV inattention subscale score in the intervention groups was 0.08 lower (0.31 lower to 0.15 higher)
ADHD inattention symptoms parent rated (SNAP-IV inattention subscale; 0-3; lower values are beneficial)	192 (1 study) 4 weeks	MODERATE ¹ due to risk of bias		The mean SNAP-IV inattention subscale score in the control groups was 1.38	The mean SNAP-IV inattention subscale score the intervention groups was 0.01 higher (0.19 lower to 0.21 higher)
ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale; 0-3; lower values are beneficial)	188 (1 study) 4 weeks	MODERATE ¹ due to risk of bias		The mean SNAP-IV hyperactivity subscale score in the control groups was 0.96	The mean SNAP-IV hyperactivity subscale score in the intervention groups was 0.03 lower (0.26 lower to 0.2 higher)
ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale; 0-3; lower values are beneficial)	188 (1 study) 4 weeks	MODERATE ¹ due to risk of bias		The mean SNAP-IV hyperactivity subscale score in the control groups was 1.11	The mean SNAP-IV hyperactivity subscale score in the intervention groups was 0.01 lower (0.2 lower to 0.18 higher)
CGI-I score of 1 or 2	189 (1 study) 4 weeks	LOW ² due to imprecision	RR 1.01 (0.75 to 1.37)	468 per 1000	10 more per 1000 (from 140 fewer to 150 more)
Discontinuation due to adverse events	183 (1 study) 4 weeks	LOW ² due to imprecision	RR 0.95 (0.06 to 14.91)	11 per 1000	1 fewer per 1000 (from 11 fewer to 156 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

Table 11: Clinical evidence summary: Lisdexamfetamine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine versus placebo (95% CI)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial; change scores reported	224 (1 study) 7 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms score in the control groups was -5.7	The mean ADHD symptom score in the intervention groups was 18.6 lower (20.98 to 16.22 lower)
Treatment Response (CGI-I); score of 1 or 2	210 (1 study) 7 weeks	MODERATE ¹ due to risk of bias	RR 5.88 (3.49 to 9.92)	123 per 1000	598 more per 1000 (from 305 more to 1000 more)
CHIP-CE academic achievement subscale; 0-100; high scores are beneficial; final values reported	221 (1 study) 7 weeks	MODERATE ¹ due to risk of bias		The mean chip-ce academic achievement score in the control groups was 29.3	The mean chip-ce academic achievement score in the intervention groups was 11 higher (8.28 to 13.72 higher)
Behaviour outcomes (WFIRS-P); 0-3; lower values are beneficial; final values given	221 (1 study) 7 weeks	MODERATE ² due to imprecision		The mean behaviour outcomes (wfirs-p) in the control groups was 1.04	The mean behaviour outcomes (wfirs-p) in the intervention groups was 0.33 lower (0.45 to 0.21 lower)
Discontinuation due to adverse events	514 (2 studies) 7 weeks	VERY LOW ^{2,3} due to imprecision, inconsistency	RR 2.44 (0.43 to 13.73)	27 per 1000	39 more per 1000 (from 5 fewer to 212 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 increment due to heterogeneity, unexplained by subgroup analysis

Table 12: Clinical evidence summary: Methylphenidate versus lisdexamfetamine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with methylphenidate versus lisdexamfetamine (95% CI)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial; change scores reported	224 (1 study) 7 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptom score in the control groups was -24.3	The mean ADHD symptom score in the intervention groups was 5.6 higher (from 2.95 higher to 8.25 higher)
Treatment Response (CGI-I scores of 1 or 2)	211 (1 study) 7 weeks	LOW ^{1,2} due to risk of bias, imprecision	RR 0.74 (0.6 to 0.91)	721 per 1000	188 fewer per 1000 (from 65 fewer to 288 fewer)
Behaviour outcomes (WFIRS-P); 0-3; lower values are beneficial; final values given)	222 (1 study) 7 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean behaviour outcomes (wfirs-p) in the control groups was 0.71	The mean behaviour outcomes (wfirs-p) in the intervention groups was 0.08 higher (0.04 lower to 0.20 higher)
CHIP-CE academic achievement subscale; 0-100; high scores are beneficial; final values reported	222 (1 study) 7 weeks	LOW ¹ due to risk of bias, imprecision		The mean chip-ce academic achievement subscale in the control groups was 40.3	The mean chip-ce academic achievement subscale in the intervention groups was 2.6 lower (5.46 lower to 0.26 higher)
Discontinuation due to adverse events	225 (1 study) 7 weeks	LOW ² due to imprecision	RR 0.44 (0.09 to 2.22)	44 per 1000	27 fewer per 1000 (from 41 fewer to 46 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 13: Clinical evidence summary: Atomoxetine versus placebo

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Atomoxetine versus placebo (95% CI)
Quality of life (Child Health Questionnaire and Child Health and Illness Profile – Child edition); 0-100, higher values are beneficial; change scores reported	391 (2 studies) 6-10 weeks	MODERATE ¹ due to risk of bias		The mean quality of life score in the control groups was 1.4	The mean quality of life scores in the intervention groups was 0.72 standard deviations higher (0.49 to 0.94 higher)
Quality of life (KINDL-R); higher values are beneficial; 0-100; final values reported	180 (1 study) 9 weeks	LOW ¹ due to risk of bias		The mean quality of life score in the control groups was 60.9	The mean quality of life score in the intervention groups was 7.9 higher (3.81 to 11.99 higher)
Treatment response (defined as 25% reduction in ABC-H and CGI-I score of 1 or 2 and ≥25% decrease on ADHD-RS)	165 (2 studies) 6-12 weeks	LOW ^{1,3} due to risk of bias, inconsistency	RR 3.91 (1.54 to 9.89)	165 per 1000	479 more per 1000 (from 89 more to 1000 more)
ADHD total symptoms (ADHD-RS, SNAP-IV and DSM-IV scale investigator rated total scores); lower values are beneficial, change scores reported	97 (3 studies) 6-9 weeks	LOW ^{1,3} due to risk of bias, inconsistency		The mean ADHD symptoms - investigator rated score in the control groups was 32.5	The mean ADHD symptoms - investigator rated score in the intervention groups was 0.71 standard deviations lower (1.35 to 0.07 lower)
ADHD total symptoms (ADHD-RS Investigator rated; SNAP-IV total scores); lower values are beneficial, final values reported	1114 (6 studies) 6-13 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms - investigator rated score in the control groups was -6.82	The mean ADHD symptoms - investigator rated score in the intervention groups was 0.47 standard deviations lower (0.75 to 0.18 lower)
ADHD total symptoms teacher rated (multiple scales including ADHD-RS, SNAP-IV total scores; lower values are beneficial, change scores reported)	746 (5 studies) 6-9 weeks	MODERATE ² due to imprecision		The mean ADHD symptoms - teacher rated score in control groups was -7.02	The mean ADHD symptoms - teacher rated score in the intervention groups was 0.58 standard deviations lower (0.74 to 0.42 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus placebo (95% CI)
ADHD total symptoms teacher rated (ADHD-RS total scores; 0-54, lower values are beneficial)	43 (1 study) 16 weeks	LOW ² due to imprecision		The mean ADHD symptoms - teacher rated score in control groups was -3.6	The mean ADHD symptoms - teacher rated score in the intervention groups was 4.66 lower (10.87 to 1.55 lower)
ADHD total symptoms (ADHD-RS total scores parent rated; CPRS total scores); lower values are beneficial; change scores	1563 (9 studies) 4-12 weeks	HIGH		The mean ADHD symptoms – parent rated score in control groups was -5.525	The mean ADHD-RS parent rated score in the intervention groups was 0.56 standard deviations lower (0.68 to 0.45 lower)
ADHD total symptoms (ADHD-RS Parent rated total scores); 0-54, lower values are beneficial; final values	72 (2 studies) 8 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms score in the control groups was 35.2	The mean ADHD symptoms score in the intervention groups was 8.01 lower (12.1 to 3.92 lower)
ADHD total symptoms (ADHD-RS Parent rated total scores); 0-54, lower values are beneficial	416 (3 studies) 12-18 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS parent rated score in the control groups was 34.8	The mean ADHD symptom score in the intervention groups was 6.98 lower (9.58 to 4.37 lower)
ADHD inattentive symptoms (ADHD-RS Inattentive subscale Investigator rated); 0-27, lower values are beneficial	538 (5 studies) 6-9 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS inattentive subscale score in the control groups was 19.9	The mean ADHD-RS inattentive subscale score in the intervention groups was 3.49 lower (44.54 to 2.45 lower)
ADHD inattentive symptoms (ADHD-RS inattentive subscale teacher rated); 0-27, Lower values are beneficial	583 (4 studies) 7-12 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS inattentive subscale score in the control groups was -3.9	The mean ADHD-RS inattentive subscale score in the intervention groups was 2.77 lower (4.07 to 1.47 lower)
ADHD inattentive symptoms	43	LOW ²		The mean ADHD-RS inattentive	The mean ADHD-RS inattentive

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus placebo (95% CI)
(ADHD-RS inattentive subscale teacher rated); 0-27, Lower values are beneficial	(1 study) 16 weeks	due to imprecision		subscale score in the control groups was -1.08	subscale score in the intervention groups was 4.16 lower (7.64 to 0.68 lower)
ADHD inattentive symptoms (ADHD-RS and CPRS Inattentive subscales parent rated; lower values are beneficial, change scores reported)	1563 (9 studies) 4-12 weeks	LOW ^{1,2} due to risk of bias, inconsistency		The mean ADHD-RS inattentive subscale – parent rated score in the control groups was -3	The mean ADHD-RS inattentive subscale parent rated in the intervention groups was 0.61 standard deviations lower (0.79 to 0.43 lower)
ADHD inattentive symptoms parent rated (ADHD-RS inattention subscale; 0-27, low values are beneficial, final values reported)	72 (2 studies) 4 weeks	LOW ¹ due to risk of bias		The mean ADHD-RS inattentive subscale – parent rated score in the control groups was 18	The mean ADHD-RS inattention subscale score in the interventions group was 4.06 lower (6.17 to 1.95 lower)
ADHD inattention symptoms (ADHD-RS Parent rated inattention subscale); 0-27, lower values are beneficial	415 (3 studies) 12-18 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS inattention subscale parent rated score in the control groups was 19.6	The mean ADHD inattention symptom score in the intervention groups was 3.6 lower (4.71 to 2.49 lower)
ADHD hyperactivity symptoms (ADHD-RS hyperactive subscale investigator rated); 0-27, lower values are beneficial	538 (5 studies) 6-9 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS hyperactivity subscale score in the control groups was -3.1	The mean ADHD-RS hyperactivity subscale score in the intervention groups was 4.87 lower (5.71 to 3.74 lower)
ADHD hyperactivity symptoms (ADHD-RS hyperactive subscale teacher rated); 0-27, lower values are beneficial	592 (4 studies) 4-12 weeks	MODERATE ³ due to inconsistency		The mean ADHD-RS hyperactivity subscale score in the control groups was 3.14	The mean ADHD-RS hyperactivity subscale score in the intervention groups was 2.53 lower (4.01 to 1.05 lower)
ADHD hyperactivity	43	LOW ² due to		The mean ADHD-RS hyperactivity	The mean ADHD-RS hyperactivity

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus placebo (95% CI)
symptoms (ADHD-RS hyperactive subscale teacher rated); 0-27, lower values are beneficial	(1 study) 16 weeks	imprecision		subscale score in the control groups was -1.08	subscale score in the intervention groups was 0.51 lower (4.62 lower to 3.6 higher)
ADHD hyperactivity symptoms (ADHD-RS and CPRS hyperactive subscale parent rated; lower values are beneficial, change scores reported)	1194 (9 studies) 4-12 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS hyperactivity subscale score in the control groups was -2.6	The mean ADHD-RS hyperactivity subscale score in the intervention groups was 0.6 standard deviations lower (0.78 to 0.42 lower)
ADHD hyperactivity symptoms parent rated (ADHD-RS hyperactivity subscale; 0-27, low values are beneficial, final values reported)	72 (2 studies) 4 weeks	VERY LOW ^{1,3} due to risk of bias, inconsistency, imprecision		The mean ADHD-RS inattentive subscale – parent rated score in the control groups was 17.1	The mean ADHD-RS hyperactivity subscale score in the interventions group was 4.16 lower (9.03 to 0.72 lower)
ADHD hyperactivity symptoms (ADHD-RS Parent rated hyperactivity subscale); 0-27, lower values are beneficial	415 (3 studies) 12-18 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS inattention subscale parent rated score in the control groups was 15.2	The mean ADHD hyperactivity symptom score in the intervention groups was 2.89 lower (4.2 to 1.58 lower)
CGI-I score of 1 or 2 (much improved or very much improved)	581 (5 studies) 4-13 weeks	MODERATE ¹ due to risk of bias	RR 1.63 (1.31 to 2.03)	275 per 1000	185 more per 1000 (from 95 more to 296 more)
Behavioural measures (ABC-H, CPRS oppositional subscale); lower values are beneficial, change scores reported	424 (2 studies) 6-12 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean behavioural scale score in the control groups was -0.525	The mean behavioural scale score in the intervention groups was 0.32 standard deviations lower (0.49 to 0.15 lower)
Behavioural measures (SNAP-IV ODD subscale,	280 (3 studies)	MODERATE ¹ due to risk of		The mean behavioural scale score in the control groups was	The mean behavioural scale score 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 Control	Risk difference with Atomoxetine versus placebo (95% CI)
CPRS oppositional subscale), lower values are beneficial, final values reported	6-12 weeks	bias		18.39	0.31 standard deviations lower (0.55 to 0.06 lower)
CHIP-PRF Achievement subscale; 0-30; high values are beneficial	149 (1 study) 12 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean CHIP-PRF achievement subscale score in the control groups was 1.55	The mean CHIP-PRF achievement subscale score in the intervention groups was 3.39 higher (0.66 lower to 7.44 higher)
Discontinuation due to adverse events	2588 (16 studies) 3-10 weeks	MODERATE ² due to imprecision	OR 1.35 (0.87 to 2.11)	33 per 1000	11 more per 1000 (from 4 fewer to 17 more)
Discontinuation due to adverse events	324 (2 studies) 12-18 weeks	LOW ² due to imprecision	RR 1.47 (0.25 to 8.71)	14 per 1000	6 more per 1000 (from 9 fewer to 84 more)
Serious adverse events	573 (3 studies) 6-10 weeks	LOW ² due to imprecision	RD 0 (-0.02 to 0.03)	0 events in control arm	0 more per 1000 (from 2 fewer to 3 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 or 2 increments because of heterogeneity, unexplained by subgroup analysis.

Table 14: Clinical evidence summary: Atomoxetine versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus methylphenidate (95% CI)
Quality of life (Child Health Questionnaire); 0-100, higher values are	147 (1 study) 6 weeks	MODERATE ¹ due to risk of bias		The mean child health questionnaire score in the control groups was 9.8	The mean child health questionnaire score in the intervention groups was 0.1 higher

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus methylphenidate (95% CI)
beneficial, final values reported					(3.67 lower to 3.87 higher)
ADHD total symptoms parent rated (ADHD symptoms – CRPS, ADHD-RS); lower values are beneficial	480 (2 studies) 6-8 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms score in the control groups was -17.55	The mean ADHD symptoms score in the intervention groups was 0.13 standard deviations higher (0.05 lower to 0.31 higher)
ADHD inattention symptoms parent rated (ADHD-RS and CPRS inattention subscales); 0-27, lower values are beneficial	490 (2 studies) 6-8 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS inattention subscale score in the control groups was -11.5	The mean ADHD-RS inattention subscale score in the intervention groups was 0.14 standard deviations higher (0.03 lower to 0.32 higher)
ADHD hyperactivity symptoms parent rated (ADHD-RS and CPRS hyperactivity subscale); 0-27, lower values are beneficial	490 (2 studies) 6-8 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS hyperactivity subscale score in the control groups was -9.1	The mean ADHD-RS hyperactivity subscale score in the intervention groups was 0 standard deviations higher (0.18 lower to 0.18 higher)
Behavioural outcomes (CPRS Oppositional subscale); 0-18, lower values are beneficial	326 (1 study) 8 weeks	MODERATE ¹ due to risk of bias		The mean behavioural score in the control groups was -3.4	The mean behavioural score in the intervention groups was 0.4 higher (0.47 lower to 1.27 higher)
Discontinuation due to adverse events	330 (1 study) 8 weeks	MODERATE ¹ due to risk of bias	RR 3.04 (1.24 to 7.46)	36 per 1000	74 more per 1000 (from 9 more to 206 more)
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 15: Clinical evidence: Atomoxetine versus guanfacine extended release

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Atomoxetine versus Guanfacine ER (95% CI)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial, change scores reported	225 (1 study) 10-13 weeks	LOW ¹ due to risk of bias, imprecision		The mean ADHD-RS score in the control groups was -23.9	The mean ADHD-RS score in the intervention groups was 8.9 higher (5.57 to 12.23 higher)
Treatment response (CGI-I score of 1 or 2)	226 (1 study) 10-13 weeks	LOW ^{1,2} due to risk of bias, imprecision	RR 0.84 (0.68 to 1.04)	667 per 1000	107 fewer per 1000 (from 213 fewer to 27 more)
Discontinuation due to adverse events	227 (1 study) 10-13 weeks	LOW ² due to imprecision	RR 0.57 (0.2 to 1.65)	78 per 1000	34 fewer per 1000 (from 63 fewer to 51 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

Table 16: Clinical evidence summary: Guanfacine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine versus placebo (95% CI)
ADHD total symptoms (investigator, ADHD-RS total scores); 0-54, lower values are beneficial	34 (1 study) 8 weeks	MODERATE ¹ due to imprecision		The mean ADHD-RS score in the control groups was 31.7	The mean ADHD-RS score in the intervention groups was 8.1 lower (16.47 lower to 0.27 higher)
ADHD inattention symptoms (investigator, ADHD-RS Inattentive subscale); 0-27, lower values are beneficial	34 (1 study) 8 weeks	MODERATE ¹ due to imprecision		The mean ADHD-RS inattentive subscale score in the control groups was 15.4	The mean ADHD-RS inattentive subscale score in the intervention groups was 2.6 lower (6.88 lower to 1.68 lower)
ADHD total symptoms (investigator, ADHD-RS	34 (1 study)	MODERATE ¹ due to		The mean ADHD-RS hyperactive subscale score in the control groups	The mean ADHD-RS hyperactive subscale score in the intervention groups

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine versus placebo (95% CI)
hyperactive subscale); 0-27, lower values are beneficial	8 weeks	imprecision		was 16.3	was 5.5 lower (10.95 lower to 0.05 lower)
CGI-I (score of 1 or 2; much improved or very much improved)	34 (1 study) 8 weeks	HIGH	OR 14.01 (3.12 – 62.88)	0 events in control arm	530 more per 1000 (from 290 more to 770 more)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 17: Clinical evidence summary: Extended release guanfacine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with ER Guanfacine versus placebo (95% CI)
ADHD symptoms investigator rated (ADHD-RS); 0-54, Lower values are beneficial; change scores reported	1587 (6 studies) 5-13 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS in the control group was -10.6	The mean ADHD-RS in the intervention groups was 6.6 lower (7.98 to 5.23 lower)
ADHD inattention symptoms investigator rated (ADHD-RS Inattentive subscale); 0-27, Lower values are beneficial, change scores and final values reported	878 (4 studies) 6-8 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS inattentive subscale - change scores in the control groups was -6.97	The mean ADHD-RS inattentive subscale score in the intervention groups was 4.02 lower (5.19 to 2.85 lower)
ADHD hyperactivity symptoms investigator rated (ADHD-RS Hyperactive/impulsive subscale); 0-54, lower values are beneficial, change scores reported	816 (3 studies) 6-8 weeks	HIGH		The mean ADHD-RS hyperactivity/impulsivity subscale - change scores in the control groups was -6.9	The mean ADHD-RS hyperactive subscale scores in the intervention groups was 3.87 lower (5.32 to 2.85 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with ER Guanfacine versus placebo (95% CI)
ADHD hyperactivity symptoms investigator rated (Aberrant Behaviour Checklist – Hyperactivity); 0-100, Lower values are beneficial, final values reported	62 (1 study) 8 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS hyperactivity/impulsivity subscale - final values in the control groups was 18.7	The mean ADHD-RS hyperactivity/impulsivity subscale - final values in the intervention groups was 8.1 lower (10.95 to 5.25 lower)
CGI-I score of 1 or 2 (much improved or very much improved)	1134 (5 studies) 5-13 weeks	MODERATE ¹ due to risk of bias	RR 1.8 (1.52 to 2.14)	321 per 1000	257 more per 1000 (from 167 more to 366 more)
Academic outcome (Weiss Functional Impairment Rating Scale Academic Performance subscale; low scores are beneficial)	333 (1 study) 8 weeks	HIGH		See comment ^a	The mean weiss functional impairment rating scale academic performance subscale score in the intervention groups was 0.34 standard deviations lower (0.54 to 0.14 lower)
Discontinuation due to adverse events	1999 (8 studies) 5-13 weeks	HIGH	RR 3.26 (2.18 to 4.87)	16 per 1000	34 more per 1000 (from 18 more to 56 more)
Serious adverse events	62 (1 study) 8 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	OR 7.9 (0.16 to 398.87)	0 events in control arm	3 more per 1000 (from 50 fewer to 120 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 increment because of heterogeneity, unexplained by subgroup analysis.
A Control group risk not reported

Table 18: Clinical evidence summary: Clonidine versus placebo

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Clonidine versus placebo (95% CI)
ADHD total symptoms parent rated (ASQ-P total scores; 0-20; lower values are beneficial)	127 (2 studies) 16 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean ADHD symptom score in the intervention groups was 3.04 lower (5.18 to 0.91 lower)
ADHD total symptoms teacher rated (ASQ-T total scores); 0-20; lower values are beneficial	126 (2 studies) 16 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptom score in the control groups was -3.2	The mean ADHD symptom score in the intervention groups was 2.21 lower (4.76 lower to 0.33 higher)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, lower values are beneficial	236 (1 study) 16 weeks	LOW due to risk of bias, imprecision		The mean ADHD symptom score in the control groups was -7.5	The mean ADHD symptom score in the intervention groups was 8.56 lower (11.5 to 5.62 lower)
ADHD inattention symptoms investigator rated (ADHD-RS inattention subscale); 0-27, lower values are beneficial, change scores reported	238 (1 study) 16 weeks	LOW due to risk of bias, imprecision		The mean ADHD inattention symptom score in the control groups was -3.4	The mean ADHD inattention symptom score in the intervention groups was 4.3 lower (6.16 to 2.44 lower)
ADHD hyperactivity symptoms (Mother/Teacher CBCL Hyperactivity subscale); 0-100, lower values are beneficial	68 (1 study) 6 weeks	HIGH		The mean mother/teacher cbcl hyperactivity subscale in the control groups was 75.8	The mean mother/teacher cbcl hyperactivity subscale in the intervention groups was 5.1 lower (5.63 to 4.57 lower)
ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactivity scores); 0-27, lower values are beneficial, change scores reported	236 (1 study) 16 weeks	LOW due to risk of bias, imprecision		The mean ADHD hyperactivity symptom score in the control groups was -4.1	The mean ADHD hyperactivity symptom score in the intervention groups was 4.52 lower (6.45 to 2.59 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Clonidine versus placebo (95% CI)
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial	126 (2 studies) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean children's global assessment scale in the intervention groups was 10.78 higher (5.93 to 15.64 higher)
Discontinued due to adverse events	250 (2 studies) 16 weeks	MODERATE ² due to imprecision	OR 3 (0.98 to 9.15)	15 per 1000	29 more per 1000 (from 0 fewer to 110 more)
Serious adverse events	236 (1 study) 16 weeks	HIGH	RD 0 (-0.02 to 0.02)	0 events in control arm	0 events in both arms

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
A control group risk not reported

Table 19: Clinical evidence summary: Clonidine versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Clonidine versus methylphenidate (95% CI)
ADHD total symptoms teacher rated (Conners ASQ-T total scores); 0-20; lower values are beneficial, change scores reported	60 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean conners ASQ-T score in the control groups was -5.07	The mean Conners ASQ-T in the intervention groups was 1.72 higher (1.48 lower to 4.92 higher)
ADHD total symptoms parent rated (Conners ASQ-P total scores); 0-20; lower values are	60 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean Conners ASQ-P score in the intervention groups was 2.5 higher (1 lower to 6 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Clonidine versus methylphenidate (95% CI)
beneficial, change scores reported					
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial	60 (1 study) 16 weeks	LOW ¹ due to risk of bias		See comment ^a	The mean children's global assessment scale in the intervention groups was 3.6 lower (9 lower to 1.8 higher)
Discontinued due to adverse events	60 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 0.94 (0.06 to 14.27)	34 per 1000	2 fewer per 1000 (from 32 fewer to 319 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
A Control group risk not reported

Table 20: Clinical evidence summary: Clonidine versus desipramine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Clonidine versus desipramine (95% CI)
ADHD hyperactivity symptoms (Mother/Teacher CBCL Hyperactivity subscale); 0-100, lower values are beneficial	68 (1 study) 6 weeks	HIGH		The mean hyperactivity score in the control groups was 68.6	The mean hyperactivity score in the intervention groups was 2.1 higher (1.48 to 2.72 higher)

Table 21: Clinical evidence summary: Clonidine versus carbamazepine

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Clonidine versus carbamazepine (95% CI)
ADHD inattention symptoms: 25% reduction in symptoms of Inattention amongst those participants with clinically significant symptoms of inattention at baseline (Vanderbilt ADHD rating scale)	22 (1 study) 4 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 2.17 (0.45 to 10.46)	154 per 1000	180 more per 1000 (from 85 fewer to 1000 more)
ADHD hyperactivity symptoms: 25% reduction in symptoms of Hyperactivity amongst those participants with clinically significant symptoms of inattention at baseline (Vanderbilt ADHD rating scale)	40 (1 study) 4 weeks	LOW ¹ due to risk of bias	RR 5.43 (1.89 to 15.56)	158 per 1000	699 more per 1000 (from 141 more to 1000 more)
ADHD impulsivity symptoms: 25% reduction in symptoms of Impulsivity amongst those participants with clinically significant symptoms of inattention at baseline (Vanderbilt ADHD rating scale)	35 (1 study) 4 weeks	LOW ¹ due to risk of bias	RR 3.54 (1.47 to 8.55)	235 per 1000	598 more per 1000 (from 111 more to 1000 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

Table 22: Clinical evidence summary: Desipramine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Desipramine versus placebo (95% CI)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, Lower values are beneficial	41 (1 study) 6 weeks	HIGH		The mean ADHD-RS score in the control groups was 42	The mean ADHD-RS score in the intervention groups was 18 lower (24.05 to 11.95 lower)
ADHD hyperactivity symptoms (Mother/Teacher CBCL Hyperactivity)	68 (1 study) 6 weeks	HIGH		The mean hyperactivity subscale score in the control groups was 75.8	The mean hyperactivity subscale score in the intervention groups was 7 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Desipramine versus placebo (95% CI)
subscale); 0-100, lower values are beneficial					(7.58 to 6.42 lower)

Table 23: Clinical evidence summary: Venlafaxine versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Venlafaxine versus methylphenidate (95% CI)
ADHD total symptoms (ADHD-RS total scores parent rated); 0-54, Lower values are beneficial	38 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean ADHD-RS - parent rated in the control groups was -16.63	The mean ADHD-RS - parent rated in the intervention groups was 2.48 higher (2.51 lower to 7.47 higher)
ADHD total symptoms (ADHD-RS total scores teacher rated); 0-54, Lower values are beneficial	38 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean ADHD-RS - teacher rated in the control groups was -15.31	The mean ADHD-RS - teacher rated in the intervention groups was 2.26 higher (1.98 lower to 6.5 higher)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 24: Clinical evidence summary: Risperidone versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus placebo (95% CI)
ADHD inattention symptoms (8 weeks PT; parent rated; CPRS inattention	84 (1 study) 8 weeks	MODERATE ¹ due to imprecision		The mean ADHD inattention symptoms score in the control groups was 2.02	The mean ADHD inattention score in the intervention groups was 0.23 lower (0.36 to 0.1 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus placebo (95% CI)
subscale; 0-3; high is poor)					
ADHD hyperactivity symptoms (8 weeks PT; parent rated; CPRS hyperactivity subscale; 0-3; high is poor)	84 (1 study) 8 weeks	MODERATE ¹ due to imprecision		The mean ADHD hyperactivity symptom score in the control groups was 1.67	The mean ADHD hyperactivity score in the intervention groups was 0.05 lower (0.15 lower to 0.05 higher)
Behavioural outcomes (ABC total scores and CPRS oppositional subscale); lower values are beneficial	122 (2 studies) 8-10 weeks	MODERATE ¹ due to imprecision		The mean behaviour score in the control groups was 19	The mean behaviour score in the intervention groups was 0.63 standard deviations lower (0.99 to 0.26 lower)
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial	39 (1 study) 24 weeks	MODERATE ¹ due to imprecision		The mean children's global assessment score in the control groups was 35.2	The mean children's global assessment score in the intervention groups was 5.74 higher (0.33 to 11.15 higher)
Serious adverse events	38 (1 study) 6 weeks	LOW ¹ due to imprecision	OR 0.14 (0.00 to 6.82)	53 per 1000	45 fewer per 1000 (from 53 fewer to 222 more)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 25: Clinical evidence summary: Aripiprazole versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aripiprazole versus placebo (95% CI)
ADHD total symptoms	41 (1 study)	LOW ^{1,2} due to risk of bias,		The mean SNAP-IV in the control groups was 0.55	The mean SNAP-IV in the intervention groups was 0.24 higher

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aripiprazole versus placebo (95% CI)
parent rated (SNAP-IV); 0-3, lower values are beneficial	6 weeks	imprecision			(0.3 lower to 0.78 higher)
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 1 MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 26: Clinical evidence summary: Buspirone versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Buspirone versus methylphenidate (95% CI)
ADHD total symptom reduction (Defined as ≥30% reduction in ADHD-RS)	34 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 0.89 (0.65 to 1.21)	875 per 1000	96 fewer per 1000 (from 306 fewer to 184 more)
ADHD total symptoms (ADHD-RS Parent rated); 0-54, lower values are beneficial	40 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS score in the control groups was -15.6	The mean ADHD-RS score in the intervention groups was 6.65 higher (1.52 to 11.78 higher)
ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial	40 (1 study) 6 weeks	MODERATE ¹ due to risk of bias		The mean ADHD-RS score in the control groups was -22.4	The mean ADHD-RS score in the intervention groups was 12.6 higher (7.27 to 17.93 higher)
Discontinuation due to adverse events	34 (1 study)	VERY LOW ^{1,2} due to risk of	OR 6.61 (0.13 to	0 events in control arm	60 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bupirone versus methylphenidate (95% CI)
	6 weeks	bias, imprecision	335.5)		(from 90 fewer to 200 more)
Serious adverse events	34 (1 study) 6 weeks	LOW ¹ due to risk of bias	RD 0.00 (-0.11 to 0.11)	0 events in control arm	0 events in both arms

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 27: Clinical evidence summary: Bupropion versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bupropion versus placebo (95% CI)
ADHD total symptoms parent rated (Conners Abbreviated Parent Questionnaire and CPTQ-P); lower values are beneficial, final values reported	124 (2 studies) 4-6 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms score in the control groups was 18.18	The mean ADHD symptoms score in the intervention groups was 0.63 standard deviations lower (1.01 to 0.25 lower)
ADHD total symptoms teacher rated (Conners Abbreviated Teacher Questionnaire and CPTQ-T); lower values are beneficial, final values reported	109 (2 studies) 4-6 weeks	MODERATE ¹ due to risk of bias		The mean ADHD symptoms score in the control groups was 19.64	The mean ADHD symptoms score in the intervention groups was 0.7 standard deviations lower (1.11 to 0.29 lower)
Discontinuation due to adverse events	139 (2 studies) 4-6 weeks	LOW ² due to imprecision	OR 4.69 (0.72 to 30.55)	0 events in control arm	50 more per 1000 (from 10 fewer to 120 more)

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bupropion versus placebo (95% CI)
at very high risk of bias					
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 28: Clinical evidence summary: Bupropion versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bupropion versus methylphenidate (95% CI)
ADHD total symptoms (PT; ADHD-RS Parent rated); 0-54, lower values are beneficial	40 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms parent rated score in the control groups was -26.2	The mean ADHD symptoms parent rated score in the intervention groups was 1.4 higher (3.38 lower to 6.18 higher)
ADHD total symptoms parent rated (Iowa Conners rating scale; crossover trial; 0-30; lower values are beneficial)	30 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms score in the control group was 9.7	The mean ADHD symptoms parent rated score in the intervention groups was 3 higher (0.76 lower to 6.76 higher)
ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial, change scores PT	40 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms teacher rated score in the control groups was -7.3	The mean ADHD symptoms parent rated score in the intervention groups was 0.5 lower (6.42 lower to 5.42 higher)
ADHD total symptoms teacher rated (Iowa Conners rating scale; crossover trial, final values; 0-30; lower values are beneficial)	30 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms score in the control group was 7.6	The mean ADHD symptoms parent rated score in the intervention groups was 3 higher (1.37 lower to 7.37 higher)
ADHD inattention symptoms (ADHD-RS	40 (1 study)	LOW ^{1,2} due to risk of		The mean ADHD symptoms inattention subscale parent rated	The mean ADHD symptoms inattention subscale parent rated

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bupropion versus methylphenidate (95% CI)
Inattention subscale - Parent rated); 0-27, lower values are beneficial; change score PT	6 weeks	bias, imprecision		score in the control groups was -12.4	score in the intervention groups was 1 higher (1.32 lower to 3.32 higher)
ADHD inattention symptoms parent rated (Iowa Conners rating scale inattention subscale; crossover trial final values; 0-15; lower values are beneficial)	30 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean inattention symptoms score in the control group was 4.4	The mean inattention symptoms parent rated score in the intervention groups was 2.4 higher (0.75 to 4.05 higher)
ADHD inattention symptoms (ADHD-RS Inattention subscale - Teacher rated); 0-27, lower values are beneficial, change scores PT	40 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean inattention subscale teacher rated score in the control groups was -3.5	The mean inattention subscale teacher rated score in the intervention groups was 0.4 lower (4.03 lower to 3.23 higher)
ADHD inattention symptoms teacher rated (Iowa Conners rating scale inattention subscale; crossover trial final values; 0-15; lower values are beneficial)	30 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean inattention symptoms score in the control group was 5.5	The mean inattention symptoms parent rated score in the intervention groups was 1.9 higher (0.75 lower to 4.55 higher)
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Parent rated); 0-27, lower values are beneficial	40 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean hyperactivity subscale - parent rated score in the control groups was -13.9	The mean hyperactivity subscale - parent rated score in the intervention groups was 0.6 higher (2.58 lower to 3.78 higher)
ADHD hyperactivity	40	LOW ²		The mean hyperactivity subscale -	The mean hyperactivity subscale -

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Bupropion versus methylphenidate (95% CI)
symptoms (ADHD-RS Hyperactivity subscale - Teacher rated); 0-27, lower values are beneficial	(1 study) 6 weeks	due to imprecision		teacher rated score in the control groups was -3.8	teacher rated score in the intervention groups was 0.1 lower (3.17 lower to 2.97 higher)
Discontinuation due to adverse events	40 (1 study) 6 weeks	LOW ² due to imprecision	RD 0.00 (-0.09 to 0.09)	0 events in control arm	0 events in both arms
Serious adverse events	40 (1 study) 6 weeks	LOW ² due to imprecision	RD 0.00 (-0.09 to 0.09)	0 events in control arm	0 events in both arms

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 29: Clinical evidence summary: Modafinil versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus placebo (95% CI)
ADHD total symptoms (ADHD-RS Parent rated); 0-54, lower values are beneficial, change scores reported	46 (1 study) 5 weeks	LOW ¹ due to risk of bias		The mean ADHD-RS - parent rated score in the control groups was -8.21	The mean ADHD-RS - parent rated score in the intervention groups was 14.26 lower (18.69 to 9.83 lower)
ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial, final values reported	68 (2 studies) 5-6 weeks	VERY LOW ^{1,3} due to risk of bias, inconsistency		The mean ADHD-RS (teacher rated) - score in the control groups was 14.7	The mean ADHD-RS (teacher rated) score in the intervention groups was 8.17 lower (22.74 lower to 6.4 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus placebo (95% CI)
Clinical global impressions – improvement (score of 1 or 2)	198 (1 study) 4 weeks	LOW ^{1,2} due to risk of bias and imprecision	RR 1.73 (0.91 to 3.29)	176 per 1000	129 more per 1000 (from 16 fewer to 404 more)
Serious adverse events	248 (1 study) 4 weeks	LOW ^{1,2} due to risk of bias, imprecision	RD 0 (-0.03 to 0.03)	0 events in control arm	0 events in both arms
Discontinued due to adverse events	248 (1 study) 4 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	OR 3.67 (0.71 – 19.00)	0 events in control arm	50 more per 1000 (from 10 more to 90 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

3 Downgraded due to heterogeneity, unexplained by subgroup analysis

Table 30: Clinical evidence summary: Modafinil versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus methylphenidate (95% CI)
ADHD total symptoms (ADHD-RS total scores Parent rated); 0-54, lower values are beneficial	60 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS - parent rated score in the control groups was -22.66	The mean ADHD-RS - parent rated score in the intervention groups was 1.7 lower (8.46 lower to 5.06 higher)
ADHD total symptoms (ADHD-	60 (1 study)	LOW ^{1,2} due to risk of bias,		The mean ADHD-RS - teacher rated score in the control groups was	The mean ADHD-RS - teacher rated score 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 Control	Risk difference with Modafinil versus methylphenidate (95% CI)
RS total scores (Teacher rated); 0-54, lower values are beneficial	6 weeks	imprecision		-21.33	0.8 higher (4.23 lower to 5.83 higher)
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 1 MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 31: Clinical evidence summary: Melatonin versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Melatonin versus placebo (95% CI)
TNO-AZL Questionnaire for Children's Health-Related Quality of Life; 0-224, higher values are beneficial, final values reported	105 (1 study) 4 weeks	HIGH		The mean quality of life score in the control groups was 176.9	The quality of life score in the intervention groups was 2.2 higher (6.28 lower to 10.68 higher)
Behavioural outcomes (Teachers Report Form); 0-100, lower values are beneficial, final values reported	105 (1 study) 4 weeks	MODERATE ¹ due to imprecision		The mean teachers report form score in the control groups was 48.1	The mean teachers report form score in the intervention groups was 6 lower (14.52 lower to 2.52 higher)
Discontinuation due to adverse effects	105 (1 study) 4 weeks	MODERATE ¹ due to imprecision	RD 0.00 (-0.04 to 0.04)	0 events in control arm	0 events in both arms
1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 32: Clinical evidence summary: Amantadine versus methylphenidate

Outcomes	No of	Quality of	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Amantadine versus methylphenidate (95% CI)
ADHD inattention symptoms (ADHD-RS Inattention subscale - Parent rated); 0-27, lower values are beneficial	38 (1 study) 6 weeks	LOW ¹ due to imprecision		The mean inattention subscale - parent rated score in the control groups was 8.45	The mean ADHD-RS inattention subscale - parent rated score in the intervention groups was 0.4 higher (4.1 lower to 4.9 higher)
ADHD inattention symptoms (ADHD-RS Inattention subscale - Teacher rated); 0-27, lower values are beneficial	38 (1 study) 6 weeks	LOW ¹ due to imprecision		The mean ADHD-RS inattention subscale - teacher rated score in the control groups was 8.6	The mean ADHD-RS inattention subscale - teacher rated score in the intervention groups was 0.2 higher (2.5 lower to 2.9 higher)
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Parent rated); 0-27, lower values are beneficial	38 (1 study) 6 weeks	LOW ¹ due to imprecision		The mean ADHD-RS hyperactivity subscale - parent rated score in the control groups was 8.8	The mean ADHD-RS hyperactivity subscale - parent rated score in the intervention groups was 0.6 higher (3.36 lower to 4.56 higher)
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Teacher rated); 0-27, lower values are beneficial	38 (1 study) 6 weeks	LOW ¹ due to imprecision		The mean ADHD-RS hyperactivity subscale - teacher rated score in the control groups was 10.35	The mean ADHD-RS hyperactivity subscale - teacher rated score in the intervention groups was 0.2 lower (3.54 lower to 3.14 higher)

1 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: Methylphenidate and clonidine versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate and clonidine versus methylphenidate (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate and clonidine versus methylphenidate (95% CI)
ADHD total symptoms; teacher rated (Conners ASQ-T total scores; 0-20; low values are beneficial)	61 (1 study) 16 weeks	LOW ¹ due to risk of bias		The mean conners asq-t in the control groups was -5.07	The mean conners asq-t in the intervention groups was 2.21 lower (5.9 lower to 1.48 higher)
ADHD total symptoms; parent rated (Conners ASQ-P total scores; 0-20; low values are beneficial)	61 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ³	The mean ADHD symptoms score the intervention groups was 3 lower (6.4 to 0.4 lower)
Behaviour (CGAS; 0-100; higher scores are beneficial)	61 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ³	The mean ADHD symptoms score the intervention groups was 2.7 higher (2.6 lower to 8 higher)
Discontinued due to adverse events	61 (1 study) 16 weeks	LOW ² due to imprecision	RR 2.72 (0.3 to 24.7)	34 per 1000	59 more per 1000 (from 24 fewer to 817 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 A control group risk not reported

Table 34: Clinical evidence summary: Methylphenidate and clonidine versus clonidine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate and clonidine versus clonidine (95% CI)
ADHD total symptoms; teacher rated (Conners ASQ-T total scores; 0-20; low	62 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean conners asq-t in the control groups was -7.28	The mean conners asq-t in the intervention groups was 4.08 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate and clonidine versus clonidine (95% CI)
values are beneficial)					(7.65 to 0.51 lower)
ADHD symptoms; parent rated (Conners ASQ-P total scores; 0-20; low values are beneficial)	63 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ³	The mean ADHD symptoms score the intervention groups was 0.9 lower (6.2 lower to 4.4 higher)
Behavioural outcome (CGAS; 0-100; higher scores are beneficial)	63 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ³	The mean ADHD symptoms score the intervention groups was 0.9 lower (6.2 lower to 4.4 higher)
Discontinued due to adverse events	62 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	OR 7.41 (0.74-74.11)	0 events in control arm	90 more per 1000 (from 20 less to 210 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Control group risk not reported

Table 35: Clinical evidence summary: Methylphenidate and clonidine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate and clonidine versus placebo (95% CI)
ADHD symptoms; teacher rated (Conners ASQ-T; 0-20; low values are	127 (2 studies) 16 weeks	VERY LOW ^{1,2} due to risk of bias,		The mean conners ASQ-T score (teacher rated) in the control groups was -3.35	The mean ADHD symptoms score the intervention groups was 5.38 lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate and clonidine versus placebo (95% CI)
beneficial)		imprecision			(7.39 to 2.87 lower)
ADHD symptoms; parent rated (Conners ASQ-P; 0-20; low values are beneficial)	127 (2 studies) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ³	The mean ADHD symptoms score the intervention groups was 5.44 lower (8.44 to 2.43 lower)
Behaviour (CGAS; 0-100; higher scores are beneficial)	127 (2 studies) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		See comment ³	The mean ADHD symptoms score the intervention groups was 12.72 higher (7.86 to 17.57 higher)
Discontinued due to adverse events	61 (1 study) 16 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 2.72 (0.3 to 24.7)	32 per 1000	52 more per 1000 (from 20 fewer to 375 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 control group risk not reported

Table 36: Clinical evidence summary: Atomoxetine and fluoxetine versus atomoxetine and placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine and fluoxetine versus atomoxetine and placebo (95% CI)
ADHD total symptoms; investigator rated (ADHD-RS total scores); 0-54; low values are beneficial	157 (1 study) 8 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS in the control groups was -20.5	The mean ADHD-RS score in the intervention groups was 3.5 lower (8.06 lower to 1.06 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine and fluoxetine versus atomoxetine and placebo (95% CI)
ADHD inattention symptoms; investigator rated (ADHD-RS inattention subscale); 0-27; low values are beneficial	157 (1 study) 8 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS inattentive subscale in the control groups was -10.7	The mean ADHD-RS inattentive subscale score in the intervention groups was 2.2 lower (4.71 lower to 0.31 higher)
ADHD hyperactivity symptoms; investigator rated (ADHD-RS hyperactivity subscale); 0-27; low values are beneficial	157 (1 study) 8 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS hyperactivity subscale in the control groups was -9.9	The mean ADHD-RS hyperactivity subscale score in the intervention groups was 1.2 lower (3.61 lower to 1.21 higher)
Discontinued due to adverse events	173 (1 study) 8 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 1.09 (0.12 to 10.19)	22 per 1000	2 more per 1000 (from 19 fewer to 163 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

1.1.3.8 Quality assessment of clinical studies included in the evidence review (adults)

Table 37: Clinical evidence summary: Immediate release Methylphenidate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Immediate release methylphenidate versus placebo (95% CI)
Treatment response	200	MODERATE ¹	RR 4.45	117 per 1000	403 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Immediate release methylphenidate versus placebo (95% CI)
(defined at a 30% decrease in AISRS and CGI-I of 1 or 2 and a decrease of at least 2 points on CGI-S and 30% reduction on DSM-IV rating scale)	(2 studies) 3-6 weeks	due to risk of bias	(2.4 to 8.25)		(from 164 more to 847 more)
ADHD total symptoms investigator rated (Barkleys ADHD Rating Scale and Conners Adult ADHD Rating Scale; lower values are beneficial, final values reported)	108 (2 studies) 3-4 weeks	LOW ^{1,3} due to risk of bias, inconsistency		The mean ADHD symptoms - final values in the control groups was 2.1	The mean ADHD symptoms - final values in the intervention groups was 0.34 standard deviations lower (0.98 lower to 0.29 higher)
ADHD total symptoms investigator rated (ADHD RS total scores); 0-54, lower values are beneficial, change scores reported	19 (1 study) 7 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms - change scores in the control groups was -12.4	The mean ADHD symptoms - change scores in the intervention groups was 2.3 higher (6.2 lower to 10.8 higher)
CGI-I score of 1 or 2 (much improved or very much improved)	65 (2 studies) 7 weeks	MODERATE ¹ due to risk of bias	RR 6.42 (2.31 to 17.85)	118 per 1000	638 more per 1000 (from 154 more to 1000 more)
Behavioural outcomes (Global Assessment of Functioning and Problem Behaviour scale); higher values are beneficial, final values reported	134 (2 studies) 2-4 weeks	MODERATE ¹ due to risk of bias		The mean behavioural outcomes in the control groups was 31.08	The mean behavioural outcomes in the intervention groups was 1.01 standard deviations higher (0.65 to 1.37 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Immediate release methylphenidate versus placebo (95% CI)
Discontinued due to adverse events	109 (2 studies) 3-7 weeks	HIGH	RD 0.04 (-0.18 to 0.27)	18 per 1000	40 more per 1000 (from 180 fewer to 270 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p> <p>3 Downgraded by 1 or 2 increments because of heterogeneity, unexplained by subgroup analysis.</p>					

Table 38: Clinical evidence summary: OROS methylphenidate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Controlled release methylphenidate versus placebo (95% CI)
Treatment response (30% reduction on WRAADS, CGI-I score of 1 or 2 and 30% reduction on AISRS)	526 (3 studies) 6-8 weeks	MODERATE ¹ due to risk of bias	RR 2.03 (1.64 to 2.51)	288 per 1000	302 more per 1000 (from 188 more to 443 more)
ADHD total symptoms investigator rated (CAARS-O:SV total scores); 0-54, lower values are beneficial, change scores reported	1150 (4 studies) 5-13 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean investigator rated ADHD symptom score in the control groups was 9	The mean investigator rated ADHD symptom score in the intervention groups was 0.38 standard deviations lower (0.50 to 0.27 lower)
ADHD total symptoms(AISRS/ADHD-RS total scores); lower values are beneficial, final values reported	124 (2 studies) 5-8 weeks	MODERATE ¹ due to risk of bias		The mean investigator rated ADHD symptoms score in the control groups was 34.7	The mean investigator rated ADHD symptom score in the intervention groups was 0.91 standard deviations lower (1.28 to 0.53 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Controlled release methylphenidate versus placebo (95% CI)
ADHD total symptoms self-rated (CAARS-O:SV and CAARS ADHD index total scores); lower values are beneficial, final values reported	50 (2 studies) 2-5 weeks	MODERATE ³ due to inconsistency		The mean self-rated ADHD symptoms score in the control groups was 57.485	The mean self-rated ADHD symptom score in the intervention groups was 0.94 standard deviations lower (2.06 to 0.19 lower)
ADHD total symptoms self-rated (CAARS total scores); 0-54, lower values are beneficial, change scores reported	757 (2 studies) 5-6 weeks	LOW ^{1,4} due to risk of bias, imprecision		The mean ADHD symptoms score in the control groups was -5.8	The mean ADHD symptoms score in the intervention groups was 6.15 lower (8.3 lower to 3.99 lower)
ADHD total symptoms self-rated (CAARS total scores); 0-54, lower values are beneficial, change scores reported	279 (1 study) 13 weeks	LOW ^{1,4} due to risk of bias, imprecision		The mean ADHD symptoms score in the control groups was -8.5	The mean ADHD symptoms score in the intervention groups was 4.2 lower (7.24 lower to 1.16 lower)
ADHD inattention symptoms investigator rated (CAARS Inattention subscale); 0-27, lower values are beneficial, change scores reported	398 (1 study) 5 weeks	LOW ^{1,4} due to risk of bias, imprecision		The mean ADHD symptoms inattention subscale in the control groups was -3.7	The mean ADHD symptoms inattention subscale in the intervention groups was 3 lower (4.24 lower to 1.76 lower)
ADHD inattention symptoms investigator rated (CAARS Inattention subscale, ADHD-RS inattention subscale); lower	114 (2 studies) 3-8 weeks	MODERATE ² due to imprecision		The mean ADHD symptoms inattention subscale in the control groups was 65.55	The mean ADHD symptoms inattention subscale in the intervention groups was 0.66 standard deviations lower (1.04 lower to 0.28 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Controlled release methylphenidate versus placebo (95% CI)
values are beneficial, final values reported					
ADHD inattention symptoms investigator rated (CAARS Inattention subscale); 0-27, lower values are beneficial	279 (1 study) 13 weeks	LOW ^{1,4} due to risk of bias, imprecision		The mean ADHD symptoms inattention subscale in the control groups was -5.5	The mean ADHD symptoms inattention subscale in the intervention groups was 2.46 lower (4.03 lower to 0.89 lower)
ADHD hyperactivity symptoms investigator rated (CAARS Hyperactive subscale); 0-27; lower values are beneficial, change scores reported	400 (1 study) 5 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms hyperactivity score in the control groups was -3.9	The mean hyperactivity subscale score in the intervention groups was 1.3 lower (2.61 lower to 0.01 higher)
ADHD hyperactivity symptoms investigator rated (CAARS and ADHD-RS hyperactivity subscales); lower values are beneficial, change scores reported	114 (2 studies) 2-8 weeks	LOW ¹ due to imprecision, inconsistency		The mean ADHD symptoms hyperactivity score in the control groups was 48.27	The mean hyperactivity subscale score in the intervention groups was 0.41 standard deviations lower (1.06 lower to 0.24 higher)
ADHD hyperactivity symptoms investigator rated (CAARS Hyperactive subscale); 0-27, lower values are beneficial, change scores	279 (1 study) 13 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD symptoms hyperactivity score in the control groups was -4.9	The mean hyperactivity subscale score in the intervention groups was 1.3 lower (2.7 lower to 0.1 higher)
CGI-I score of 1 or 2	474	MODERATE ¹	RR 2.02	217 per 1000	220 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Controlled release methylphenidate versus placebo (95% CI)
(much improved or very much improved)	(3 studies) 7-13 weeks	due to risk of bias	(1.52 to 2.67)		(from 140 more to 300 more)
Behavioural outcomes (Global Assessment of Functioning); 0-100, higher values are beneficial	30 (1 study) 5 weeks	HIGH		The mean global assessment of functioning in the control groups was 39.4	The mean global assessment of functioning in the intervention groups was 15.8 higher (8.17 to 23.43 higher)
Emotional dysregulation (PT; CAARS-S:L Emotional Lability Scale); 0-12; lower values are beneficial, final values reported	359 (1 study) 5 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean caars-s:l emotional lability scale in the control groups was 8.2	The mean caars-s:l emotional lability scale in the intervention groups was 1.3 lower (2.29 to 0.31 lower)
Emotional dysregulation (crossover trial; WRAADS emotional dysregulation subscale); 0-28; lower values are beneficial	94 (1 study) 4 weeks	MODERATE ² due to imprecision		The mean emotional dysregulation score in the control groups was 20	The mean emotional dysregulation score in the intervention groups was 6.5 lower (9.68 to 3.32 lower)
Discontinued due to adverse events	2000 (9 studies) 6-13 weeks	HIGH	OR 3.02 (2.08 to 4.38)	28 per 1000	52 more per 1000 (from 28 more to 84 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 39: Clinical evidence summary: Dexamphetamine versus placebo

Outcomes	No of	Quality of the	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Dexamphetamine versus placebo (95% CI)
ADHD total symptoms investigator rated (DSM-IV RS total scores); 0-54; lower values are beneficial, final values reported	76 (2 studies) 2 weeks	MODERATE ¹ due to imprecision		The mean investigator rated ADHD symptom score in the control groups was 31.6	The mean investigator rated ADHD symptom score in the intervention groups was 7.71 lower (12.63 to 2.79 lower)
ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial, final values reported	76 (2 studies) 2 weeks	MODERATE ¹ due to imprecision		The mean investigator rated inattentive subscale score in the control groups was 16.9	The mean investigator rated inattentive subscale score in the intervention groups was 4.53 lower (7.07 to 2 lower)
ADHD hyperactive symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial, final values reported	76 (2 studies) 2 weeks	MODERATE ¹ due to imprecision		The mean investigator rated hyperactive subscale score in the control groups was 12.7	The mean investigator rated hyperactive subscale score in the intervention groups was 3.11 lower (5.93 to 0.3 lower)
CGI-I score of 1 or 2 (much improved or very much improved)	45 (1 study) 6 weeks	MODERATE ² due to risk of bias	OR 14.31 (4.1 to 50.01)	0 events in control arm	583 more per 1000 (from 380 more to 787 more)
<p>1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs. 2 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</p>					

Table 40: Clinical evidence summary: Lisdexamfetamine dimesylate versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine dimesylate versus placebo (95% CI)
Quality of life (AAQoL); 0-100, higher values are beneficial	161 (1 study) 10 weeks	VERY LOW ^{1,3} due to risk of bias, imprecision		See comment ^a	The mean quality of life score in the intervention groups was 14,70 higher (5.90 to 23.50 higher)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, lower values are beneficial, change scores reported	635 (3 studies) 4-10 weeks	MODERATE ¹ due to risk of bias		The mean investigator rated ADHD-RS score in the control groups was 7.5	The mean ADHD-RS score in the intervention groups was 10.51 lower (12.71 to 8.31 lower)
ADHD inattention symptoms investigator rated;(ADHD-RS inattention subscale); 0-27, lower values are beneficial	153 (1 study) 10 weeks	LOW ¹ due to risk of bias		The mean investigator rated ADHD-RS score in the control groups was - 6.1	The mean inattention subscale score in the intervention groups was 6.1 lower (8.26 to 3.94 lower)
ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactivity subscale); 0-27, lower values are beneficial	153 (1 study) 10 weeks	LOW ¹ due to risk of bias		The mean ADHD-RS score in the control groups was -4.2	The mean hyperactivity/impulsivity subscale score in the intervention groups was 5 lower (6.8 to 3.2 lower)
CGI-I score of 1 or 2 (much improved or very much improved)	420 (1 study) 4 weeks	MODERATE ¹ due to risk of bias	RR 1.99 (1.34 to 2.97)	290 per 1000	287 more per 1000 (from 99 more to 572 more)
Behavioural outcomes (global assessment of functioning); 0-100, high values are beneficial	61 (1 study) 6 weeks	LOW ^{1,3} due to risk of bias, imprecision		The mean CGAS score in the control groups was 58.9	The mean CGAS score in the intervention group was 4.6 higher (2.29 to 6.91 higher)
Discontinuation due to adverse events	577 (3 studies)	VERY LOW ^{1,3} due to risk of bias,	RR 2.19 (0.72 to	24 per 1000	24 more per 1000 (from 6 fewer to 97 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine dimesylate versus placebo (95% CI)
	4-10 weeks	imprecision	6.66)		
<p>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</p> <p>2 The majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)</p> <p>3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p> <p>A Control group risk not report</p>					

Table 41: Clinical evidence summary: Atomoxetine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus placebo (95% CI)
Quality of life (AAQoL); 0-100; higher values are beneficial	906 (3 studies) 10-12 weeks	MODERATE ¹ due to risk of bias		The mean quality of life score in the control groups was 10.25	The mean quality of life in the intervention groups was 4.72 higher (2.66 to 6.77 higher)
Quality of life (AAQoL); 0-100; higher values are beneficial	648 (2 studies) 16-24 weeks	LOW ¹ due to risk of bias		The mean quality of life score in the control groups was 11.1	The mean quality of life score in the intervention groups was 4.04 higher (1.55 to 6.54 higher)
ADHD total symptoms (multiple scales including AISRS and ADHD-RS total scores; Investigator rated); lower values are beneficial, change scores reported	872 (5 studies) 8-12 weeks	VERY LOW ^{1,2,3} due to risk of bias, imprecision, inconsistency		The mean caars total score - investigated rated in the control groups was -7.8	The mean ADHD symptoms investigator rated score in the intervention groups was 0.7 standard deviations lower (1.07 to 6.54 lower)
ADHD total symptoms	530	VERY		The mean investigated rated ADHD	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 Control	Risk difference with Atomoxetine versus placebo (95% CI)
(CAARS and AISRS total scores; Investigator rated); lower values are beneficial, final values reported	(2 studies) 8-12 weeks	LOW ^{1,2,3} due to risk of bias, imprecision, inconsistency		symptom score in the control groups was 22.9	investigator rated score in the intervention groups was 0.82 standard deviations lower (1.8 to 0.16 lower)
ADHD total symptoms investigator rated (CAARS and AISRS total score; Investigator rated); 0-54, lower values are beneficial	1429 (3 studies) 16-24 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean investigated rated ADHD symptom score in the control groups was -8.3	The mean ADHD symptoms investigator rated score in the intervention groups was 0.37 standard deviations lower (0.47 to 0.27 lower)
ADHD total symptoms (CAARS total score - Self rated); 0-84, lower values are beneficial, change scores reported	831 (2 studies) 10-12 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean self-rated ADHD symptoms score in the control groups was -8.3	The mean self-rated ADHD symptoms score in the intervention groups was 4.83 lower (6.27 to 3.39 lower)
ADHD inattention symptoms (CAARS Inattention subscale - Self rated); 0-27, lower values are beneficial, change scores reported	831 (2 studies) 10-12 weeks	VERY LOW ^{1,2,3} due to risk of bias, imprecision, inconsistency		The mean caars inattention subscale - self rated in the control groups was -4.75	The mean caars inattention subscale self-rated in the intervention groups was 2.53 lower (3.33 to 1.72 lower)
ADHD inattention symptoms (multiple scales including CAARS inattention subscale - Investigator rated); lower values are beneficial, change scores reported	1763 (6 studies) 8-12 weeks	VERY LOW ^{1,2,3} due to risk of bias, imprecision and inconsistency		The mean self-rated inattention score investigator rated in the control groups was -4.2	The mean caars inattention subscale - investigator rated in the intervention groups was 0.44 standard deviations lower (0.61 to 0.26 lower)
ADHD inattention symptoms (CAARS and AISRS Inattention subscale -	1044 (3 studies) 16-24 weeks	LOW ^{1,2} due to risk of bias,		The mean inattention subscale score investigator rated in the control groups was -4.4	The mean caars inattention subscale - investigator rated score 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 Control	Risk difference with Atomoxetine versus placebo (95% CI)
Investigator rated); lower values are beneficial		imprecision			0.37 standard deviations lower (0.6 to 0.14 lower)
ADHD hyperactivity symptoms (CAARS and AISRS Hyperactivity/impulsivity subscale - Investigator rated); lower values are beneficial, change scores reported	1763 (6 studies) 8-12 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean caars hyperactivity/impulsivity subscale - investigator rated in the control groups was -3.72	The mean caars hyperactivity/impulsivity subscale - investigator rated in the intervention groups was 0.38 standard deviations lower (0.48 to 0.28 lower)
ADHD hyperactivity symptoms (CAARS Hyperactivity/impulsivity subscale - Self rated); 0-27, lower values are beneficial, change scores reported	831 (2 studies) 10-12 weeks	MODERATE ¹ due to risk of bias		The mean self-rated hyperactivity score d in the control groups was -3.55	The mean self-rated hyperactivity score in the intervention groups was 2.21 lower (2.83 to 1.29 lower)
ADHD hyperactivity symptoms (AISRS and CAARS Hyperactivity/impulsivity subscale - Investigator rated); lower values are beneficial	1044 (3 studies) 16-24 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean hyperactivity/impulsivity subscale score in the control groups was -3.9	The mean investigator rated hyperactivity/impulsivity subscale in the intervention groups was 0.34 standard deviations lower (0.34 to 0.22 lower)
Behavioural outcomes (BRIEF-A Self Report total score); 0-100; lower values are beneficial; change scores reported	716 (2 studies) 10-12 weeks	LOW ¹ due to risk of bias		The mean brief-a self report total score in the control groups was -9.76	The mean brief-a self report total score in the intervention groups was 4.92 lower (7.1 to 2.73 lower)
Discontinuation due to adverse events	1729 (7 studies) 8-14 weeks	MODERATE ¹ due to risk of bias	OR 2.3 (1.53 to 3.47)	33 per 1000	40 more per 1000 (from 17 more to 73 more)
Discontinuation due to adverse	502	MODERATE ¹	RR 2.26	94 per 1000	118 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine versus placebo (95% CI)
events	(1 study) 24 weeks	due to risk of bias	(1.43 to 3.58)		(from 40 more to 243 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Downgraded by 1 increment because of heterogeneity, unexplained by subgroup analysis.
A Control group risk not reported

Table 42: Clinical evidence summary: Guanfacine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine versus placebo (95% CI)
ADHD total symptoms investigator rated (DSM-IV RS); 0-54; lower values are beneficial	34 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean investigator rated ADHD symptoms score in the control groups was 30.4	The mean investigator rated ADHD symptoms score in the intervention groups was 8.1 lower (14.47 to 1.73 lower)
ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial	34 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean investigator rated symptoms inattentive score in the control groups was 17.2	The mean investigator rated inattentive score in the intervention groups was 4.4 lower (7.55 to 1.25 lower)
ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are	34 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean investigator rated hyperactive score in the control groups was 13.2	The mean investigator rated hyperactive score in the intervention groups was 3.7 lower (7.56 lower to 0.16 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine versus placebo (95% CI)
beneficial					
1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 43: Clinical evidence summary: Guanfacine versus dexamphetamine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine versus dexamphetamine (95% CI)
ADHD total symptoms investigator rated(DSM-IV RS total scores); 0-54; lower values are beneficial	34 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean investigator rated ADHD symptoms score in the control groups was 24.2	The mean investigator rated ADHD symptoms score in the intervention groups was 1.9 lower (8.81 lower to 5.01 higher)
ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial	34 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean investigator rated inattentive score in the control groups was 14	The mean investigator rated inattentive score in the intervention groups was 1.2 lower (4.69 lower to 2.29 higher)
ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial	34 (1 study) 6 weeks	LOW ¹ due to imprecision		The mean investigator rated hyperactive score in the control groups was 10.2	The mean investigator rated hyperactive score in the intervention groups was 0.7 lower (4.56 lower to 3.16 higher)
1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.					

Table 44: Clinical evidence summary: Reboxetine versus placebo

Outcomes	No of	Quality of	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Reboxetine versus placebo (95% CI)
ADHD total symptoms investigator rated (CAARS total scores); 0-54, lower values are beneficial	39 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean investigator rated ADHD symptom score in the control groups was 27.47	The mean investigator rated ADHD symptom score in the intervention groups was 5.58 lower (11.18 lower to 0.02 higher)
ADHD inattention symptoms investigator rated (CAARS Inattentive subscale); 0-27; lower values are beneficial	39 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean investigator rated inattentive score in the control groups was 16.05	The mean investigator rated inattentive score in the intervention groups was 4.74 lower (7.83 to 1.65 lower)
ADHD hyperactivity symptoms investigator rated (CAARS Hyperactivity subscale); 0-27; lower values are beneficial	39 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean investigator rated hyperactivity score in the control groups was 11.47	The mean investigator rated hyperactivity score in the intervention groups was 0.93 lower (4.12 lower to 2.26 higher)
Behavioural outcomes (Global Assessment of Functioning); 0-100, higher values are beneficial	39 (1 study) 6 weeks	LOW ¹ due to risk of bias		The mean global assessment of functioning in the control groups was 5.05	The mean global assessment of functioning in the intervention groups was 1.08 lower (0.68 to 1.48 lower)
Discontinuation due to adverse events	40 (1 study) 6 weeks	LOW ² due to imprecision	RR 1.48 (0.15 to 15)	59 per 1000	28 more per 1000 (from 50 fewer to 824 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

Table 45: Clinical evidence summary: Venlafaxine versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Venlafaxine versus placebo (95% CI)
ADHD total symptoms self-rated (CAARS ADHD index); 0-27, lower values are beneficial	41 (1 study) 6 weeks	MODERATE ¹ due to risk of bias		The mean self-rated ADHD index score in the control groups was -12.05	The mean self-rated ADHD index score in the intervention groups was 13.3 lower (19.34 to 7.26 lower)
ADHD inattention symptoms self-rated (CAARS Inattentive subscale); 0-27, lower values are beneficial	41 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean self-rated inattentive score in the control groups was -14.65	The mean self-rated inattentive subscale in the intervention groups was 8.7 lower (14.21 to 3.19 lower)
ADHD hyperactivity symptoms self-rated (CAARS Hyperactive/Impulsive subscale); 0-27, lower values are beneficial	41 (1 study) 6 weeks	MODERATE ¹ due to risk of bias		The mean self-rated hyperactive/impulsive score in the control groups was -11.35	The mean self-rated hyperactive/impulsive score in the intervention groups was 15.25 lower (22.19 to 8.31 lower)
Discontinuation due to adverse events	44 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	OR 7.39 (0.15 to 372.38)	0 events in control arm	44 more per 1000 (from 71 fewer to 163 more)
Serious adverse events	44 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision	RD 0.00 (-0.08 to 0.08)	0 events in control arm	0 events in both arms

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 46: Clinical evidence summary: Bupropion versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with SR Bupropion versus placebo (95% CI)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, lower values are beneficial, change scores	22 (1 study) 7 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS in the control groups was -12.4	The mean ADHD-RS in the intervention groups was 1.3 lower (8.77 lower to 6.17 higher)
ADHD total symptoms investigator rated (CAARS total scores); 0-54, lower scores are beneficial, final values reported	42 (1 study) 6 weeks	MODERATE ² due to imprecision		The mean CAARS in the control groups was 34.43	The mean CAARS in the intervention groups was 10.72 lower (18.57 to 2.87 lower)
CGI score of 1 or 2	22 (1 study) 7 weeks	LOW ^{1,2} due to risk of bias, imprecision	RR 2.33 (0.81 to 6.76)	273 per 1000	363 more per 1000 (from 52 fewer to 1000 more)
Discontinuation due to adverse events	22 (1 study) 7 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	OR 0.14 (0 to 6.82)	91 per 1000	77 fewer per 1000 (from 91 fewer to 315 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 47: Clinical evidence summary: Bupropion versus methylphenidate

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with SR Bupropion versus methylphenidate (95% CI)
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54 lower values are beneficial	19 (1 study) 7 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD-RS in the control groups was -10.1	The mean ADHD-RS in the intervention groups was 3.6 lower (10.65 lower to 3.45 higher)
CGI-I score of 1 or 2 (much	19	VERY LOW ^{1,2}	RR 1.27	500 per 1000	135 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with SR Bupropion versus methylphenidate (95% CI)
improved or very much improved)	(1 study) 7 weeks	due to risk of bias, imprecision	(0.56 to 2.9)		(from 220 fewer to 950 more)
Discontinued due to adverse events	19 (1 study) 7 weeks	LOW ^{1,2} due to risk of bias, imprecision	OR 0.08 (0 to 1.45)	250 per 1000	224 fewer per 1000 (from 250 fewer to 76 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 48: Clinical evidence summary: Modafinil versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus placebo (95% CI)
Quality of Life (Quality of life enjoyment and satisfaction questionnaire); 0-10, higher values are beneficial	193 (1 study) 9 weeks	LOW ¹ due to risk of bias		The mean quality of life score in the control groups was 4.4	The mean quality of life score in the intervention groups was 1.38 higher (1.35 lower to 4.11 higher)
ADHD total symptoms (Adult ADHD self-report scores); 0-54, lower values are beneficial	193 (1 study) 9 weeks	LOW ¹ due to risk of bias		The mean self-reported ADHD symptoms score in the control groups was -12.2	The mean self-reported ADHD symptoms score in the intervention groups was 3.73 lower (8.31 to 0.85 lower)
ADHD total symptoms investigator rated (DSM IV RS total scores); 0-54, lower values are beneficial	42 (1 study) 2 weeks	MODERATE ² due to imprecision		The mean investigator rated ADHD symptoms score in the control groups was 28.8	The mean investigator rated ADHD symptoms score in the intervention groups was 10.5 lower (16.92 to 4.08 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus placebo (95% CI)
ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27, lower values are beneficial	42 (1 study) 2 weeks	HIGH		The mean investigator rated inattentive score in the control groups was 16.6	The mean investigator rated inattentive score in the intervention groups was 6.1 lower (9.02 to 3.18 lower)
ADHD hyperactivity symptoms investigator rated (DSM IV RS Hyperactive subscale); 0-27, lower values are beneficial	42 (1 study) 2 weeks	MODERATE ² due to imprecision		The mean ADHD symptoms hyperactive subscale in the control groups was 12.2	The mean ADHD symptoms hyperactive subscale in the intervention groups was 4.9 lower (8.89 to 0.91 lower)
Behavioural outcome (BRIEF-A); 0-100; lower values are beneficial	192 (1 study) 9 weeks	LOW ¹ due to risk of bias		The mean brief-a score in the control groups was -8.1	The mean brief-a in the intervention groups was 3.11 lower (7.25 to 1.03 higher)
Discontinuation due to adverse events	338 (1 study) 9 weeks	LOW ¹ due to risk of bias	RR 3.22 (1.46 to 7.13)	81 per 1000	180 more per 1000 (from 110 more to 260 more)

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 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 49: Clinical evidence summary: Modafinil versus dexamphetamine

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus dexamphetamine (95% CI)
ADHD total symptoms	42 (1 study)	MODERATE ¹ due to		The mean investigator rated ADHD symptoms score in the control groups	The mean investigator rated ADHD symptoms score in the intervention

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Modafinil versus dexamphetamine (95% CI)
investigator rated (DSM-IV total scores); 0-54, lower values are beneficial	2 weeks	imprecision		was 20	groups was 1.7 lower (8.5 lower to 5.1 higher)
ADHD inattention symptoms investigator rated (DSM-IV Inattentive subscale); 0-27, lower values are beneficial, final values reported	42 (1 study) 2 weeks	LOW ¹ due to imprecision		The mean investigator rated inattentive score in the control groups was 11	The mean investigator rated inattentive score in the intervention groups was 0.5 lower (4.15 lower to 3.15 higher)
ADHD hyperactivity symptoms investigator rated (DSM-IV Hyperactive subscale); 0-27, lower values are beneficial, final values reported	42 (1 study) 2 weeks	MODERATE ¹ due to imprecision		The mean investigator rated hyperactive score in the control groups was 9	The mean investigator rated hyperactive score in the intervention groups was 1.7 lower (5.28 lower to 1.88 higher)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 50: Clinical evidence summary: Atomoxetine and bupirone versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine and bupirone versus placebo (95% CI)
ADHD total symptoms investigator rated (AISRS total scores); 0-54; lower values are beneficial	244 (1 study) 8 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean ADHD symptoms (aisrs) in the intervention groups was 4.8 lower (7.74 to 1.86 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Atomoxetine and bupirone versus placebo (95% CI)
ADHD inattention symptoms investigator rated inattention subscale (AISRS); 0-27; lower values beneficial	244 (1 study) 8 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean ADHD symptoms inattention subscale (aisrs) in the intervention groups was 1.6 lower (3.56 lower to 0.36 higher)
ADHD hyperactivity symptoms investigator rated hyperactivity subscale (AISRS); 0-27; lower values beneficial	244 (1 study) 8 weeks	LOW ^{1,2} due to risk of bias, imprecision		See comment ^a	The mean ADHD symptoms hyperactivity subscale (aisrs) in the intervention groups was 3.24 lower (5.63 to 0.85 lower)
Discontinued due to adverse events	144 (1 study) 8 weeks	LOW ² due to imprecision	RR 1.04 (0.45 to 2.37)	149 per 1000	6 more per 1000 (from 82 fewer to 204 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p> <p>A control group risk not reported</p>					

See appendix F for full GRADE tables.

1 **1.1.4 Economic evidence**

2 **1.1.4.1 Included studies**

3 **1.1.4.1.1 2008 guideline literature**

4 One study from CG72 was included in this review³⁷¹

5 The included study can be found in **Table 51**.

6 **1.1.4.1.2 Published literature**

7 Two health economic studies were identified in children with the relevant comparison and
8 have been included in this review.^{188, 331} One economic evaluation was also identified in
9 adults.⁷¹⁶

10 One study on children was from the UK and used a decision model to compare an algorithm
11 with atomoxetine as first line treatment versus an algorithm of standard treatment (without
12 atomoxetine) in different subgroup populations (only the medication naïve group have been
13 included in this review question).

14 The second study on children adapted the model from the UK study to a Spanish context,
15 however it compared a sequence of atomoxetine as first line versus atomoxetine as second
16 line (and did not include dexamphetamine in the sequence). Therefore the interventions were
17 different, and it only looked at some of the subgroups that the UK paper looked at (again only
18 some of which are included in this review), therefore the models were felt sufficiently different
19 to be included as separate studies.

20 Note that although these studies compare sequences in different ways, they are both
21 essentially asking which drug you should start with.

22 The adult study was from the UK and used a decision model to compare lisdexamfetamine
23 with atomoxetine or extended release methylphenidate.

24 These are summarised in the health economic evidence profiles below (**Table 52, Table 53**)
25 and the health economic evidence tables in Appendix H.

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

27 **1.1.4.2 Excluded studies**

28 Five studies^{211, 249, 277, 356, 472, 717} from CG72, all in children, have been selectively excluded
29 due to limited applicability and/or methodological limitations.

30 These are listed in Appendix I, with reasons for exclusion given.

31

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

33

1.1.4.3 Summary of studies included in the economic evidence review

Table 51: Health economic evidence profile: [2008 guideline included economic evaluations]

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
King 2006 ³⁷¹ (UK)	Directly applicable (a)	Potentially serious limitations(b)	<p>1 year decision tree model comparing 37 strategies in total, consisting of 18 possible sequences of three active treatments, (18 respective sequences of combination therapies were included in a sensitivity analysis), plus no treatment strategies could include;</p> <p>Methylphenidate- IR, Methylphenidate- MR-8 hours, Methylphenidate- MR-12 hours, Atomoxetine, Dexamfetamine, plus all the above medications combined with behavioural therapy.</p> <p>Effectiveness based on 6 trials include in an NMA. Cost components include; drug costs, resource use associated with responders and non-responders (psychiatrist, paediatrician, and GP consultations, and a blood test). Resource use associated non responders.</p> <p>Uses EQ-5D.</p>	See evidence table as too many comparators to report.	See evidence table as too many comparators to report.	A strategy of; DEX – IR-MPH – ATX – NT was dominant	<p>PSA undertaken (number of simulations not reported).</p> <p>Probability strategy is cost-effective (£30K threshold): 31% when considering all 38 strategies, but 60% when comparing only the 19 strategies that have 3 active treatments per strategy.</p> <p>A number of sensitivity analyses were undertaken testing structural assumptions and inputs, in some cases the results changed to the below strategy being optimal; IR-MPH – DEX – ATX – NT</p>

THIS STUDY WAS UPDATED BY THE GUIDELINE HEALTH ECONOMIST (BY REPLICATING THE STUDY AS DESCRIBED FROM THE PAPER) TO INCLUDE UP TO DATE COSTS GIVEN THE LARGE PRICE INCREASE IN DEXAMFETAMINE PRICE.

MOST COST EFFECTIVE = A STRATEGY OF; IR-MPH – DEX – ATX – NT

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
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(ICER = £485 VS NO TREATMENT) – see discussion following these tables for more detail.

Abbreviations: NMA = Network meta-analysis; QALY: quality-adjusted life years; LDX = Lisdexamfetamine; IR-MPH: Immediate release methylphenidate; ER-MPH: extended release methylphenidate, ATX = Atomoxetine; DEX: Dexamfetamine; NT: no treatment

(a) UK study, uses EQ-5D.

(b) Based on limited clinical data. Some of the studies excluded subjects who were known non-responders to stimulant therapy (which is contrary to the guideline clinical review which excluded those studies). Assumed independence of treatments in the sequence. Based on doses from the trials which may not represent doses in practice.

Table 52: Health economic evidence profile: [Children; first line Atomoxetine algorithm versus standard treatment algorithm or second line atomoxetine algorithm]

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Cottrell 2008 ¹⁸⁸ (UK)	Partially applicable ^(a)	Potentially serious limitations ^(b)	<p>Markov model of 1 year time horizon with monthly cycles. Population is children with ADHD. Health states are based on response to treatment and adverse events. How response was defined in the trials is not reported. Based on various RCT evidence. Some of which excluded from the clinical review. Models different sequences and patients move to the next treatment if they fail the current one.</p> <p>2 out of the 5 subgroups evaluated in the study are included in this review question as they are groups 'with no history of pharmacotherapy use':</p> <ul style="list-style-type: none"> • Subgroup 1: Stimulant naïve patients <ul style="list-style-type: none"> ○ a treatment algorithm of atomoxetine →IR-MPH→IR- 	<p>Subgroup 1 (includes IR-MPH): £408.34</p> <p>Subgroup 1 (includes XR-MPH): £265.71</p> <p>Subgroup 2: £480.94</p>	<p>Subgroup 1 (includes IR-MPH): 0.0268</p> <p>Subgroup 1 (includes XR-MPH): 0.0201</p> <p>Subgroup 2: 0.0417</p>	<p>Subgroup 1 (includes IR-MPH): £15,244</p> <p>Subgroup 1 (includes XR-MPH): £13,241</p> <p>Subgroup 2: £11,523</p>	<p>Uncertainty around the ICER not reported. Paper states a probabilistic analysis was done but data on this is not reported.</p> <p>Multiple sensitivity analyses are stated as being undertaken however results are not reported.</p> <p>Model most sensitive to the utility values used. ICER rose to beyond the threshold when the difference between the utilities for the different treatments was reduced.</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			<p>DEX→no treatment, with the comparator being the same sequence but without atomoxetine</p> <ul style="list-style-type: none"> ○ same as above except IR-MPH is replaced with XR-MPH. • Subgroup 2: Stimulant contraindicated (naive) <ul style="list-style-type: none"> ○ atomoxetine followed by no treatment if that fails, compared to no treatment alone. 				
Hong 2009 ³³¹ (Spain)	Partially applicable ^(c)	Potentially serious limitations ^(d)	<p>Markov model of 1 year time horizon with monthly cycles. Population is children with ADHD. Health states are based on response to treatment and adverse events. How response was defined in the trials is not reported. Based on various RCT evidence. Some of which excluded from the clinical review. Models different sequences and patients move to the next treatment if they fail the current one.</p> <p>2 out of the 3 subgroups evaluated in the study are included in this review question as they are groups 'with no history of pharmacotherapy use':</p> <ul style="list-style-type: none"> • Subgroup 1: Stimulant naïve patients: <ul style="list-style-type: none"> ○ a treatment algorithm of atomoxetine →IR-MPH→no 	<p>Subgroup 1 (includes IR-MPH)^(e): £615</p> <p>Subgroup 1 (includes XR-MPH): £277</p> <p>Subgroup 2: £876</p>	<p>Subgroup 1 (includes IR-MPH): 0.02</p> <p>Subgroup 1 (includes XR-MPH): 0.013</p> <p>Subgroup 2: 0.042</p>	<p>Subgroup 1 (includes IR-MPH): £31,007</p> <p>Subgroup 1 (includes XR-MPH): £21,971</p> <p>Subgroup 2: £21,079</p>	<p>Uncertainty around the ICER not reported. Paper states a probabilistic analysis was done but data on this is not reported.</p> <p>Multiple sensitivity analyses are stated as being undertaken however results are not reported.</p> <p>Model most sensitive to the utility values used. ICER increased dramatically when the difference between the utilities for the different treatments was reduced.</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			treatment versus IR-MPH → atomoxetine → no treatment <ul style="list-style-type: none"> ○ same as above except IR-MPH is replaced with XR-MPH. • Subgroup 2: Stimulant naïve patients with contraindications <ul style="list-style-type: none"> ○ atomoxetine compared to no treatment. 				

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial, IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine

(a) UK study with an NHS cost perspective. However; population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.

(b) Potential conflict of interest. Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. Based on some data that has been excluded for this question. No adverse event costs or other resource use costs included.

(c) Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.

(d) Potential conflict of interest. Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. No adverse event costs or other resource use costs included. Based on some data that has been excluded for this question.

(e) 2008 Spanish Euros converted to GBP using purchasing power parities. The incremental cost was calculated by the health economist after converting the cost of each treatment strategy into GBP's.

Table 53: Health economic evidence profile: [Adults; Lisdexamfetamine versus Atomoxetine or extended release Methylphenidate]

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Zimovetz 2017 ⁷¹⁵ (UK)	Directly applicable (a)	Potentially serious limitations(b)	Decision tree model with a 1 year time horizon comparing lisdexamfetamine with ER methylphenidate and atomoxetine in adults. An NMA informs treatment effect and discontinuation risks. Costs also include resource use associated with response and non-response. Uses EQ-5D.	LDX vs ATX = -£195 LDX vs ER-MPH = -£9	LDX vs ATX = 0.01 LDX vs ER-MPH = 0.006	LDX dominant LDX dominant	PSA with 5000 simulations. Probability LDX cost effective at £20,000; vs ATX = 80%, vs ER-MPH = 61% Additional sensitivity analyses showed that the results when

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
							compared to MPH was sensitive to discontinuation rates. LDX remained dominant compared to ATX in all sensitivity analyses.

Abbreviations: NMA = Network meta-analysis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; LDX = Lisdexamfetamine; ER-MPH: extended release methylphenidate, ATX = Atomoxetine.

(c) UK study, uses EQ-5D.

(d) Potential conflict of interest. No additional treatment assumed following non response/discontinuation. NMA methods a combination of dichotomous outcomes and continuous transformed to dichotomous. Some studies in their NMA we haven't included in our review. Methods sometimes unclear; resource use estimates. No adverse event costs included

1 Since the previous guideline, the price of dexamfetamine has substantially increased. This is
2 likely to affect the conclusions of all included economic studies with dexamfetamine, as
3 they are out of date with the costs.

4 King et al 2006³⁷¹ was replicated using the information in the study, to see what impact
5 updating the cost of the interventions would have. The original base case result of King 2006
6 showed that the most cost effective strategy was;

7 Dexamfetamine – Methylphenidate IR – Atomoxetine – No treatment.

8 This was also the case when the model was replicated without changing the drug costs. This
9 added reassurance that the replication was similar to the original model (although some
10 assumptions had to be made based on the information provided in the paper in order to
11 replicate the model).

12 After updating the model to include up to date drug prices, the most cost effective option
13 was;

14 Methylphenidate IR – Atomoxetine – Dexamfetamine – No treatment.

15 This shows that keeping all other parts of the model the same except for updating the drug
16 prices is having an impact of the results enough to change the conclusions. The increased
17 price of dexamfetamine means that it is no longer cost effective first or second line even
18 though it has a higher response rate and fewer withdrawals than the other drugs. The
19 increased cost is outweighing the additional benefit.

20 Note that the same limitations of the model remain as the purpose of this exercise was only
21 to see the impact of the price changes and structural and data aspects of the model cannot
22 be altered as it is not an original guideline model. Notable limitations include that the
23 treatments in the sequence are independent of each other which is unlikely to reflect reality,
24 and also the limited number of sources informing the clinical effect.

25 Cottrell 2008 also included dexamfetamine in the sequences evaluated. This study had 5
26 subgroups, which had different sequences for the intervention and comparator of each
27 subgroup depending on previous history with stimulants. As the purpose of this study is to
28 estimate the costs and benefits of atomoxetine versus other treatments, then the intervention
29 arm for each subgroup always had atomoxetine first followed by other treatments, and the
30 comparator sequence was the same sequence but without atomoxetine.

31 For example for a stimulant naïve population the treatments being evaluated are a sequence
32 of; ATX - IR MPH - IR DEX - no treatment, versus; IR MPH - IR DEX - no treatment.

33 Because of this, dexamfetamine will always be closer to the front of the sequence in the
34 comparator arm. Meaning that in the comparator arm, more people will be on dexamfetamine
35 because you only go on to the next treatment if you fail the previous one. Therefore a
36 dexamfetamine price increase will increase the total cost of the comparator arm more than
37 the total cost of the intervention arm, therefore making the incremental cost smaller and the
38 intervention arm more cost effective. It may even make the intervention cost saving. These
39 are assumptions about what the impact will be, but it has been shown from the update of the
40 King model that sequences with dexamfetamine lower down the treatment line are likely to
41 be more cost effective than sequences with dexamfetamine nearer the front of the sequence,
42 because of the higher price of dexamfetamine.

43 **1.1.4.4 Unit costs**

44 Relevant unit costs are provided below to aid consideration of cost-effectiveness. The drugs
45 listed below are based on those identified from the clinical review as well as those commonly

1 used even if the review did not find evidence on them, and therefore do not include the entire
2 list of interventions from the protocol.

3 Where several studies evaluated the same intervention, or the dose was lower than the
4 maximum recommended by the BNF (only for drugs licensed for ADHD), both low and high
5 doses are presented to reflect the range of costs possible. Conservative estimates have
6 been used whereby the highest doses of those reported in the studies /recommended in the
7 BNF have been used. Note that there can be various generic versions of a drug, but drugs of
8 the same class with the same dose have the same cost regardless of who manufactures it.

9 **Table 54: UK costs of ADHD drugs for children**

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source of dose
Methylphenidate hydrochloride					
Methylphenidate	Low dose: 30mg per day	10mg tablet (pack of 30) = £5.49	£16.70	£200.39	Clinical review
Methylphenidate	High dose: 60mg per day	20mg tablet (pack of 30) = £10.92	£33.22	£398.58	BNF max dose
Concerta XL (modified release methylphenidate)	Low dose: 18mg per day	18mg tablet (pack of 30) = £31.19	£31.62	£379.48	Clinical review
Concerta XL (modified release methylphenidate)	High dose: 54mg per day	36mg tablet (pack of 30) = £42.45	£64.56	£774.71	BNF max dose
Equasym XL (modified release methylphenidate)	Low dose: 20mg per day	10mg capsule (pack of 30) = £25.00	£50.69	£608.33	Estimate of low dose
Equasym XL (modified release methylphenidate)	High dose: 60 mg per day	30mg capsule (pack of 30) = £35.00	£70.97	£851.67	BNF max dose
Atomoxetine					
Strattera	Low dose: 40 mg per day	40mg tablet (pack of 28) = £53.09	£57.67	£692.07	Clinical review
	High dose: 100 mg per day	As above	£144.18	£1,730.17	Clinical review
Dexamfetamine					
Dexamfetamine	20mg per day	5mg tablet (pack of 28) = £24.75	£107.54	£1,290.54	BNF
		10mg tablet (pack of 30)	£80.67	£967.98	
Lisdexamfetamine					
Elvanse	50mg per day	50 mg capsule (pack of 28)	£74.52	£894.25	Clinical review

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source of dose
		= £68.60			
Other drugs					
Guanfacine hydrochloride (modified release)	4mg per day	2mg tablet (pack of 28) = £58.52	£127.14	£1,525.70	Clinical review
Clonidine hydrochloride (Catapres)	400 micrograms per day ^(a)	100 microgram tablet (pack of 112) = £8.04	£8.73	£104.81	Clinical review
Risperidone	2mg per day	1mg tablet (pack of 20) = £0.80	£2.43	£29.20	Clinical review
Amantadine hydrochloride	150mg per day	100mg tablet (pack of 56) = £41.00	£33.40	£400.85	Clinical review
Melatonin (Circadin) (modified release)	6mg per day	2mg tablet (pack of 30) = £15.39	£46.81	£561.74	Clinical review
Bupropion hydrochloride (modified release) (Zyban)	150mg per day	150mg tablet (pack of 60) = £41.76	£21.17	£254.04	Clinical review
Modafinil	300mg per day	100mg tablet (pack of 30) = £5.88	£17.89	£214.62	Clinical review
Buspirone hydrochloride	30mg per day	10mg tablet (pack of 30) = £4.63	£14.08	£169.00	Clinical review
Aripiprazole	20mg per day	10mg tablet (pack of 28) = £2.77	£6.02	£72.22	Clinical review
Venlafaxine hydrochloride	75mg per day	37.5mg tablet (pack of 56) = £2.04	£2.22	£26.59	Clinical review

Source: BNF ('Drug tariff' price), May 2016, with dexamfetamine new dose available of 10mg sourced in May 2017.

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

Note that where higher doses are being considered, tablets with higher dose formulations have been used as these tend to have economies of scale as less tablets are also needed.

Table 55: 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	Low dose: 40mg per day	20mg tablet (pack of 30) = £10.92	£22.14	£265.72	Clinical review

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source of dose
Methylphenidate	High dose: 120mg per day	As above	£66.43	£797.16	Clinical review
Concerta XL (modified release methylphenidate)	Low dose: 72mg per day	18mg tablet (pack of 30) = £31.19	£126.49	£1,517.91	Clinical review
Concerta XL (modified release methylphenidate)	High dose: 108mg per day	54mg tablet ^(a) (pack of 30) = £60.48	£122.64	£1,471.68	BNF max dose
Equasym XL (modified release methylphenidate)	Low dose: 40mg per day	20mg capsule (pack of 30) = £30.00	£60.83	£730.00	Estimate of low dose
Equasym XL (modified release methylphenidate)	High dose: 100mg per day	30mg capsule (pack of 30) = £35.00	£118.29	£1,419.44	BNF max dose
Atomoxetine					
Strattera	Low dose: 40 mg per day	40mg per day (pack of 28) = £53.09	£57.67	£692.07	Clinical review
Strattera	High dose: 100mg per day	As above	£144.18	£1,730.17	Clinical review
Lisdexamfetamine dimesylate					
Elvanse	Low dose: 30 mg per day	30mg tablet (pack of 28) = £58.24	£63.27	£759.20	Clinical review
Elvanse	High dose: 70 mg per day	50mg tablet (pack of 28) = £68.60	£104.33	£1,251.95	Clinical review
Dexamfetamine sulfate					
Dexamfetamine sulfate	40mg per day	5mg tablet (pack of 28) = £24.75	£215.09	£2,581.07	Clinical review
		10mg tablet (pack of 28) = £39.78	£161.33	£1,935.96	
Other drugs					
Guanfacine hydrochloride (modified release)	4mg per day	2mg tablet (pack of 28) = £58.52	£127.14	£1,525.70	Estimate based on children's dose
Bupropion hydrochloride (modified release)	300 mg per day	150mg tablet (pack of 60) = £41.76	£42.34	£508.08	Clinical review
Reboxetine (Edronax)	8mg per day	4mg tablet (pack of 60) = £18.91	£19.17	£230.07	Clinical review

Drug	Daily dose (or unit or total)	Cost (per unit)	Cost – monthly	Cost – annual	Source of dose
Venlafaxine hydrochloride	225 mg per day	37.5mg tablet (pack of 56) = £2.04	£6.65	£79.78	Clinical review

Source: BNF ('Drug tariff' price), May 2016, with dexamfetamine new dose available of 10mg sourced in May 2017.

(a) Where a large dose is required, a formulation with a higher dose per tablet has being used in the costing, if available, to ensure a reasonable number of tablets are taken to meet the dose specified.

The pricing structure of the different drugs can also impact the overall cost, as if you are taking a higher dose 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 then 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 is illustrated below.

Table 56: Staff costs associated with selecting and monitoring medication treatment

Staff	Costs	Source
Psychiatric Consultant	£107 per hour	PSSRU 2015
Band 5 nurse	£36 per hour	PSSRU 2015

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.

1.1.5 Resource impact

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

1.1.6 Evidence statements

1.1.6.1 Clinical evidence statements

231.1.6.1.1 Children under 5

Methylphenidate versus placebo

- No evidence was identified for quality of life, CGI-I, serious adverse events or discontinuation due to adverse events. No evidence was identified for any of the important outcomes except behavioural outcomes measured by the children's global assessment scale.
- There was a clinically important benefit of methylphenidate for ADHD symptoms total (parent-teacher composite; 1 study very low quality) (parent rated; 1 study low quality) and behavioural symptoms (1 study low quality)

Risperidone versus methylphenidate

- 1 • No evidence was identified for quality of life, CGI-I or serious adverse events. No
2 evidence was identified for any of the important outcomes.
- 3 • There was no clinical difference between risperidone and methylphenidate on total,
4 inattentive and hyperactivity ADHD symptoms (parent rated; 1 study very low quality).
- 5 • The number of children discontinuing their medication due to adverse events was lower
6 for risperidone compared to methylphenidate, and this was clinically important (1 study
7 very low quality).

8 **Risperidone and methylphenidate versus methylphenidate**

- 9 • No evidence was identified for quality of life. No evidence was identified for any of the
10 important outcomes except behavioural outcomes measured by the CPRS oppositional
11 subscale.
- 12 • There was no clinical difference on total, inattention and hyperactivity ADHD symptoms
13 and behaviour outcomes as reported by parents (1 study very low quality).
- 14 • There was a clinically important benefit of methylphenidate and risperidone combined on
15 CGI-I (1 study very low quality).
- 16 • There was clinically important harm of risperidone and methylphenidate combined on
17 discontinuation due to adverse events (1 study low quality).

181.1.6.1.2 **Children and young people aged 5 to 18**

19 **Immediate release (IR) methylphenidate versus placebo**

- 20 • No evidence was identified for quality of life, or serious adverse events. No evidence for
21 any of the important outcomes except behavioural outcomes measured by children's
22 Global assessment scale.
- 23 • There was a clinically important benefit of methylphenidate for ADHD total symptoms
24 (parent rated; 2 studies low quality) (teacher rated; 2 studies low quality) (teacher rated; 1
25 study moderate quality), ADHD inattention symptoms (parent rated; 1 study moderate
26 quality) (teacher rated; 1 study moderate quality), ADHD hyperactivity symptoms (teacher
27 rated, 3 studies low to moderate quality), CGI-I (3 studies moderate quality), behavioural
28 outcomes (2 studies low quality).
- 29 • There was no clinical difference for ADHD symptoms total (parent rated; 3 studies
30 moderate quality), ADHD hyperactivity symptoms (parent rated; 1 study low quality)
31 (teacher rated; 1 study low quality), discontinuation due to adverse events (4 studies low
32 quality) and serious adverse events (1 study moderate quality).

33 **OROS Methylphenidate versus placebo**

- 34 • No evidence was identified for serious adverse events. No evidence was identified for
35 any of the important outcomes except for behavioural outcomes and academic
36 achievement.
- 37 • There was a clinically important benefit of methylphenidate for quality of life (1 study low
38 quality), total ADHD symptoms (parent rated; 2 studies moderate quality) (teacher rated; 1
39 study moderate quality) (investigator rated 1 study moderate quality), ADHD inattention
40 symptoms (parent rated; 2 studies moderate quality) (teacher rated; 2 studies low quality)
41 (investigator rated; 1 study very low quality), ADHD hyperactivity symptoms (parent rated;
42 2 studies moderate quality) (teacher rated; 2 studies moderate quality) (investigator rated;
43 1 study very low quality), CGI-I (2 studies moderate quality), behavioural outcomes (1
44 study low quality) and academic achievement (1 study low quality).
- 45 • There was no clinical difference in the number of children discontinuing their medication
46 due to adverse events (3 studies low quality).

47 **IR methylphenidate versus OROS methylphenidate**

- 1 • No evidence was identified for quality of life, serious adverse events or any of the
2 important outcomes.
- 3 • There was no clinically important difference for ADHD inattention symptoms (teacher
4 rated; 1 study moderate quality) (parent rated; 1 study moderate quality), ADHD
5 hyperactivity symptoms (teacher rated; 1 study moderate quality) (parent rated; 1 study
6 moderate quality), CGI-I (1 study low quality) and discontinuation due to adverse events
7 (1 study low quality).

8 **Lisdexamfetamine versus placebo**

- 9 • No evidence was identified for quality of life, inattentive or hyperactivity ADHD symptoms
10 or serious adverse events. No evidence for any of the important outcomes except
11 behaviour outcomes as measured by the WFIRS-P scale and academic achievement as
12 measured by the CHIP-CE academic achievement subscale.
- 13 • There was a clinically important benefit of lisdexamfetamine for ADHD total symptoms
14 (investigator rated; 1 study moderate quality), CGI-I, academic achievement and
15 behaviour outcomes (1 study moderate quality).
- 16 • There was no clinical difference for discontinuation due to adverse events (2 studies very
17 low quality).

18 **Methylphenidate versus lisdexamfetamine**

- 19 • No evidence was identified for quality of life, inattentive or hyperactivity ADHD symptoms
20 and serious adverse events. No evidence for any of the important outcomes except
21 behaviour outcomes as measured by the WFIRS-P scale and academic achievement as
22 measured by the CHIP-CE academic achievement subscale.
- 23 • There was a clinically important benefit of lisdexamfetamine for ADHD total symptoms
24 (investigator rated; 1 study moderate quality) and CGI-I (1 study, low quality).
- 25 • There was no clinical difference for discontinuation due to adverse events, academic
26 achievement and behaviour outcomes (1 study low quality).
- 27 •

28 **Atomoxetine versus placebo**

- 29 • No evidence for any of the important outcomes except behavioural outcomes measured
30 by various scales and academic achievement measured by the CHIP-PRF achievement
31 subscale.
- 32 • There was a clinically important benefit of atomoxetine for quality of life (2 studies
33 moderate quality) (1 study low quality), treatment response (2 studies low quality), ADHD
34 total symptoms (investigator rated; 3 studies low quality) (investigator rated; 6 studies
35 moderate quality) (teacher rated; 5 studies moderate quality) (teacher rated; 1 study low
36 quality) (parent rated; 9 studies high quality) (parent rated; 2 studies low quality) (parent
37 rated; 3 studies moderate quality), ADHD inattention symptoms (investigator rated; 5
38 studies low quality) (teacher rated; 5 studies low quality) (parent rated; 9 studies low
39 quality) (parent rated; 2 studies low quality) (parent rated; 3 studies moderate quality),
40 ADHD hyperactivity symptoms (investigator rated; 5 studies moderate quality) (teacher
41 rated; 4 studies moderate quality) (teacher rated; 1 study low quality) (parent rated; 12
42 studies moderate quality) (parent rated; 2 studies very low quality), CGI-I (5 studies
43 moderate quality) and behavioural outcomes (2 studies low quality).
- 44 • There was no clinical difference for behavioural outcomes (3 studies moderate quality),
45 academic achievement (1 study low quality), discontinuation due to adverse events (16
46 studies moderate quality) (2 studies low quality) and serious adverse events (3 studies
47 low quality).

48 **Atomoxetine versus methylphenidate**

- 1 • No evidence was identified for CGI-I or serious adverse events. No evidence for any of
2 the important outcomes except behavioural outcomes measured on the CPRS
3 oppositional subscale.
4 • There was no clinical differences for quality of life (1 study moderate quality), total,
5 inattentive and hyperactivity ADHD symptoms (parent rated; 2 studies moderate quality)
6 or behavioural outcomes (1 study moderate quality). More children discontinued
7 atomoxetine due to adverse events compared to methylphenidate (1 study moderate
8 quality).

9 **Atomoxetine versus guanfacine extended release**

- 10 • No evidence was identified for quality of life, serious adverse events or any important
11 outcomes.
12 • There was a clinically important benefit of guanfacine for ADHD total symptoms
13 (investigator rated; 1 study low quality), CGI-I (1 study low quality)
14 • There was no clinically important difference in the number of children discontinuing due to
15 adverse events (1 study low quality).

16 **Guanfacine versus placebo**

- 17 • No evidence was identified for quality of life, discontinuation due to adverse events or
18 serious adverse events. No evidence for any of the important outcomes.
19 • There was a clinically important benefit of guanfacine for total and hyperactivity ADHD
20 symptoms (investigator rated; 1 study moderate quality) and CGI-I scores (1 study high
21 quality).
22 • There was no clinically important difference for ADHD inattention symptoms (investigator
23 rated; 1 study moderate quality).

24 **Extended release Guanfacine versus placebo**

- 25 • No evidence was identified for quality of life. No evidence for any of the important
26 outcomes except for academic achievement as measured by the WFIRS academic
27 performance subscale.
28 • There was a clinically important benefit of extended release guanfacine for total ADHD
29 symptoms (investigator rated; 6 studies low quality), ADHD inattention symptoms
30 (investigator rated; 4 studies low quality), ADHD hyperactivity symptoms (investigator
31 rated; 5 studies high to moderate quality) and CGI-I scores (5 studies moderate quality).
32 • There was clinically important harm of extended release guanfacine for serious adverse
33 events (1 study very low quality); 1 participant in the guanfacine arm had a serious
34 adverse event, compared to zero in the placebo arm.
35 • There was no clinically important difference for academic outcomes (1 study high quality)
36 and discontinuation due to adverse events (8 studies high quality).

37 **Clonidine versus placebo**

- 38 • No evidence was identified for quality of life or CGI-I. No evidence for any of the important
39 outcomes except for behavioural outcomes, as measured by CGAS.
40 • There was a clinically important benefit of clonidine for ADHD total symptoms (parent
41 rated; 2 studies low quality) (teacher rated; 2 studies low quality) (investigator rated; 1
42 study low quality), ADHD inattention symptoms (investigator rated; 1 study low quality)
43 and hyperactivity symptoms (investigator rated, 1 study low quality) (parent/teacher rated;
44 1 study high quality) and behaviour outcomes (2 studies very low quality).
45 • There was no clinical difference for discontinuation due to adverse events (2 studies
46 moderate quality) or serious adverse events (1 study high quality).

47 **Clonidine versus methylphenidate**

- 1 • The only evidence identified was on ADHD total symptoms, discontinuation due to
2 adverse events and behavioural outcomes, as measured by CGAS.
3 • There was a clinically important benefit of methylphenidate for ADHD total symptoms
4 (teacher rated; 1 study very low quality) (parent rated; 1 study very low quality).
5 • There was no clinical difference for behavioural outcomes (1 study low quality) or in
6 discontinuation rates due to adverse events (1 study very low quality).

7 **Clonidine versus desipramine**

- 8 • The only evidence identified was on ADHD hyperactivity symptoms.
9 • There was a clinically important benefit of desipramine for ADHD hyperactivity symptoms
10 (parent/teacher rated; 1 study high quality).

11 **Clonidine versus carbamazepine**

- 12 • The only evidence identified was on ADHD symptoms.
13 • There was a clinically important benefit of clonidine for ADHD inattention symptoms
14 (investigator rated; 1 study very low quality), ADHD hyperactivity symptoms (investigator
15 rated; 1 study low quality) and ADHD impulsivity symptoms (investigator rated; 1 study
16 low quality).

17 **Desipramine versus placebo**

- 18 • The only evidence identified was on total ADHD symptoms.
19 • There was a clinically important benefit of desipramine for ADHD total symptoms
20 (investigator rated; 1 study high quality) and ADHD hyperactivity symptoms
21 (parent/teacher rated; 1 study high quality).

22 **Venlafaxine versus methylphenidate**

- 23 • The only evidence identified was for total ADHD symptoms.
24 • There was no clinical difference in ADHD total symptoms (parent and teacher rated; 1
25 study moderate quality).

26 **Risperidone versus placebo**

- 27 • No evidence was identified for quality of life, CGI-I, ADHD total symptoms and
28 discontinuation due to adverse events. No evidence for any of the important outcomes
29 except for behavioural outcomes as measured by multiple scales including CGAS.
30 • There was a clinically important benefit of risperidone for behaviour outcomes (1 study
31 moderate quality) and serious adverse events (1 study low quality).
32 • There was no clinical difference for ADHD inattention and hyperactivity symptoms (parent
33 rated; 1 study moderate quality) or behavioural outcomes measured by the ABC and
34 CPRS oppositional subscale (2 studies moderate quality).

35 **Aripiprazole versus placebo**

- 36 • The only evidence identified was for ADHD total symptoms.
37 • There was clinically important harm of aripiprazole for ADHD total symptoms (parent rated;
38 1 study low quality).

39 **Buspirone versus methylphenidate**

- 40 • The only evidence identified was for ADHD total symptoms, discontinuation due to
41 adverse events and serious adverse events.
42 • There was a clinically important benefit of methylphenidate for ADHD total symptoms
43 (parent rated; 2 studies low to very low quality) (teacher rated; 1 study moderate quality).
44 • There was clinically important harm of buspirone for discontinuation due to adverse
45 events (1 study very low quality).

- 1 • There was no clinical difference for serious adverse events (1 study low quality).

2 **Bupropion versus placebo**

- 3 • The only evidence identified was for ADHD total symptoms and discontinuation due to
4 adverse events.
5 • There was a clinically important benefit of bupropion for ADHD total symptoms (parent
6 and teacher rated, 2 studies moderate quality).
7 • There was clinically important harm of bupropion for discontinuation due to adverse
8 events (2 studies low quality).

9 **Bupropion versus methylphenidate**

- 10 • The only evidence identified was for ADHD symptoms, serious adverse events and
11 discontinuation due to adverse events.
12 • There was a clinically important benefit of methylphenidate for ADHD total symptoms
13 (parent rated; 2 studies low quality) (teacher rated; 1 study low quality), ADHD inattention
14 symptoms (parent rated; 1 study low quality).
15 • There was no clinical difference for ADHD total symptoms (teacher rated; 1 study low
16 quality), ADHD inattention symptoms (parent rated; 1 study low quality) (teacher rated, 1
17 study low quality), ADHD hyperactivity symptoms (parent rated; 1 study very low quality)
18 (teacher rated; 1 study low quality), discontinuation due to adverse events (1 study low
19 quality) and serious adverse events (1 study low quality).

20 **Modafinil versus placebo**

- 21 • No evidence was identified for quality of life or ADHD hyperactivity or inattention
22 symptoms. No evidence for any important outcomes.
23 • There was a clinically important benefit of modafinil for ADHD total symptoms (parent
24 rated; 1 study low quality) (teacher rated; 2 studies very low quality) and CGI-I (1 study
25 low quality).
26 • There was no clinical difference for serious adverse events (1 study low quality).
27 • There was clinically important harm of modafinil for discontinuation due to adverse events
28 (1 study very low quality).

29 **Modafinil versus methylphenidate**

- 30 • The only evidence identified was for ADHD total symptoms.
31 • There was no clinical difference for total symptoms (parent and teacher rated; 1 study low
32 quality).

33 **Melatonin versus placebo**

- 34 • The only evidence identified was for quality of life, discontinuation due to adverse events
35 and behavioural outcomes as measured by the Teachers Report Form.
36 • There was no clinical difference for quality of life, behavioural outcomes or discontinuation
37 due to adverse events (1 study moderate to high quality).

38 **Amantadine versus methylphenidate**

- 39 • The only evidence identified was for ADHD inattention and hyperactivity symptoms.
40 • There was no clinical difference for ADHD inattention or hyperactivity symptoms (parent
41 and teacher rated; 1 study low quality).

42 **Methylphenidate and clonidine versus methylphenidate**

- 43 • The only evidence identified was for ADHD total symptoms, behaviour outcomes
44 (measured by CGAS) and discontinuation due to adverse events.
45 • There was a clinically important benefit of ADHD total symptoms (parent and teacher
46 rated; 1 study low to very low quality), and behaviour outcomes (1 study very low quality).

- 1 • There was clinically important harm of methylphenidate and clonidine combined for
2 discontinuation due to adverse events (1 study low quality).

3 **Methylphenidate and clonidine versus clonidine**

- 4 • The only evidence identified was for ADHD total symptoms, behaviour outcomes
5 (measured by CGAS) and discontinuation due to adverse events.
6 • There was a clinically important benefit of methylphenidate and clonidine combined for
7 ADHD total symptoms (parent and teacher rated; very low quality), and behaviour
8 outcomes (1 study very low quality).
9 • There was no clinical difference for discontinuation due to adverse events (1 study very
10 low quality).

11 **Methylphenidate and clonidine versus placebo**

- 12 • The only evidence identified was for ADHD total symptoms, behaviour outcomes
13 (measured by CGAS) and discontinuation due to adverse events.
14 • There was a clinically important benefit of methylphenidate and clonidine for ADHD total
15 symptoms (parent and teacher rated; 2 studies very low quality), and behaviour outcomes
16 (2 studies very low quality).
17 • There was clinically important harm of methylphenidate and clonidine combined for
18 discontinuation due to adverse events (1 study very low quality).

19 **Atomoxetine and fluoxetine versus atomoxetine**

- 20 • The only evidence identified was for ADHD symptoms and discontinuation due to adverse
21 events.
22 • There was a clinically important benefit of atomoxetine and fluoxetine combined for ADHD
23 inattention symptoms (investigator rated; 1 study very low quality).
24 • There was no clinical difference for ADHD total and hyperactivity symptoms (investigator
25 rated; 1 study very low quality) or discontinuation due to adverse events (1 study very low
26 quality).

27 **271.1.6.1.3 Adults**

28 **Immediate release methylphenidate versus placebo**

- 29 • There was no evidence identified for quality of life or serious adverse events. No evidence
30 for important outcomes except for behaviour outcomes, as measured by the global
31 assessment of functioning and problem behaviour scale.
32 • There was a clinically important benefit of methylphenidate for ADHD total symptoms
33 (investigator rated; 3 studies very low to moderate quality), treatment response (2 studies
34 low quality) and CGI-I (2 studies moderate quality).
35 • There was clinically important harm of methylphenidate for discontinuation due to adverse
36 events (2 studies high quality).
37 • There was no clinical difference for behaviour outcomes (2 studies moderate quality).

38 **OROS methylphenidate versus placebo**

- 39 • There was no evidence for quality of life or serious adverse events.
40 • There was a clinically important benefit of methylphenidate for treatment response (3
41 studies moderate quality), ADHD total symptoms (investigator rated; 4 studies low quality)
42 (investigator rated; 2 studies moderate quality) (self-rated, 2 studies moderate quality)
43 (self-rated; 2 studies low quality) (self-rated; 1 study low quality), ADHD inattention
44 symptoms (investigator rated; 1 study low quality) (investigator rated; 1 study low quality),
45 ADHD hyperactivity symptoms (investigator rated; 2 studies low quality), CGI-I (3 studies
46 moderate quality) and behaviour outcomes (1 study high quality), emotional dysregulation
47 (1 study moderate quality).

- 1 • There was no clinical difference for ADHD inattention symptoms (investigator rated; 2
2 studies moderate quality), ADHD hyperactivity symptoms (investigator rated; 2 studies low
3 quality) and emotional dysregulation (1 study very low quality).
4 • There was clinically important harm of methylphenidate for discontinuation due to adverse
5 events (9 studies high quality).

6 **Dexamphetamine versus placebo**

- 7 • The only evidence identified was for ADHD symptoms and CGI-I.
8 • There was a clinically important benefit of methylphenidate for ADHD total, inattention and
9 hyperactivity symptoms (investigator rated; 2 studies moderate quality) and CGI-I (1 study
10 moderate quality).

11 **Lisdexamfetamine versus placebo**

- 12 • No evidence was identified for serious adverse events. No evidence for important
13 outcomes except for behaviour outcomes, as measured by the GAF scale,
14 • There was a clinically important benefit of methylphenidate for ADHD total symptoms
15 (investigator rated; 3 studies moderate quality), ADHD inattention symptoms (investigator
16 rated; 1 study low quality), ADHD hyperactivity symptoms (investigator rated; 1 study low
17 quality), CGI-I (1 study moderate quality) and behaviour outcomes (1 study low quality).
18 • There was no clinical difference for quality of life (1 study very low quality) or
19 discontinuation due to adverse events (3 studies very low quality).

20 **Atomoxetine versus placebo**

- 21 • There was no evidence for CGI-I or serious adverse events.
22 • There was a clinically important benefit of atomoxetine for quality of life (5 studies low to
23 moderate quality), ADHD total symptoms (investigator rated, 10 studies low to very low
24 quality) (self-rated; 2 studies low quality), ADHD inattention symptoms (self-rated; 2
25 studies low quality) (investigator rated; 9 studies low to very low quality) and ADHD
26 hyperactivity symptoms (investigator rated; 9 studies very low quality) (self-rated, 2
27 studies moderate quality).
28 • There was clinically important harm of atomoxetine for discontinuation due to adverse
29 events at 24 weeks (1 study moderate quality).
30 • There was no clinical difference for behaviour outcomes (2 studies low quality) or
31 discontinuation due to adverse events up to 14 weeks (7 studies moderate quality).

32 **Guanfacine versus placebo**

- 33 • The only evidence identified was for ADHD symptoms.
34 • There was a clinically important benefit of guanfacine for ADHD total, inattention and
35 hyperactivity symptoms (investigator rated; 1 study moderate quality).

36 **Guanfacine versus dexamphetamine**

- 37 • The only evidence identified was for ADHD symptoms.
38 • There was no clinical difference of ADHD total, inattention or hyperactivity symptoms
39 (investigator rated; 1 study low to moderate quality)

40 **Reboxetine versus placebo**

- 41 • The only evidence identified was for ADHD symptoms, discontinuation due to adverse
42 events and behaviour outcomes as measured by the GAF scale.
43 • There was a clinically important benefit of reboxetine for ADHD total symptoms
44 (investigator rated; 1 study low quality), ADHD inattention symptoms (investigator rated; 1
45 study very low quality) and behaviour outcomes (1 study low quality).
46 • There was no clinical difference for ADHD hyperactivity symptoms (1 study very low
47 quality) or discontinuation due to adverse events (1 study low quality).

1 **Venlafaxine versus placebo**

- 2 • The only evidence identified was for ADHD symptoms, discontinuation due to adverse
3 events and serious adverse events.
- 4 • There was a clinically important benefit of venlafaxine for ADHD total, inattention and
5 hyperactivity symptoms (self-rated; 1 study low to moderate quality).
- 6 • There was no clinical difference for discontinuation due to adverse events (1 study very
7 low quality) or serious adverse events (1 study low quality).

8 **Bupropion versus placebo**

- 9 • The only evidence identified was for ADHD total symptoms, CGI-I and discontinuation due
10 to adverse events.
- 11 • There was a clinically important benefit of bupropion for ADHD total symptoms
12 (investigator rated, 1 study moderate quality), CGI-I (1 study low quality) and
13 discontinuation due to adverse events (1 study very low quality)
- 14 • There was no clinical difference for ADHD total symptoms (investigator rated, 1 study very
15 low quality)

16 **Bupropion versus methylphenidate**

- 17 • The only evidence identified was for ADHD total symptoms, CGI-I and discontinuation due
18 to adverse events.
- 19 • There was a clinically important benefit of bupropion for ADHD total symptoms
20 (investigator rated, 1 study low quality), CGI-I (1 study very low quality) and
21 discontinuation due to adverse events (1 study low quality).

22 **Modafinil versus placebo**

- 23 • There was no evidence identified for CGI-I, serious adverse events or emotional
24 dysregulation.
- 25 • There was a clinically important benefit of modafinil for ADHD total symptoms (self-rated;
26 1 study low quality) (investigator rated; 1 study moderate quality), ADHD inattention
27 symptoms (investigator rated; 1 study high quality) and ADHD hyperactivity symptoms
28 (investigator rated; 1 study moderate quality).
- 29 • There was clinically important harm of modafinil for discontinuation due to adverse events
30 (1 study low quality).
- 31 • There was no clinical difference for quality of life (1 study low quality) or behaviour
32 outcomes (1 study low quality).

33 **Modafinil versus dexamphetamine**

- 34 • The only evidence identified was for ADHD symptoms.
- 35 • There was no clinical difference for ADHD total, inattention and hyperactivity symptoms
36 (investigator rated; 1 study moderate to low quality).

37 **Atomoxetine and buspirone versus placebo**

- 38 • The only evidence identified was for ADHD symptoms and discontinuation due to adverse
39 events.
- 40 • There was a clinically important benefit of atomoxetine and buspirone for ADHD total
41 symptoms (investigator rated; 1 study low quality).
- 42 • There was no clinical difference for ADHD inattention or hyperactivity symptoms
43 (investigator rated; 1 study low quality) or discontinuation due to adverse events (1 study
44 low quality).

1.1.6.2 Health economic evidence statements

- One cost-utility analysis found that a sequence of; Dexamfetamine – [methylphenidate-IR] – atomoxetine – no treatment, was dominant compared to other sequences of drugs for treating ADHD in children. This analysis was assessed as partially applicable with potentially serious limitations.

This analysis was adapted with up to date intervention costs and found that a sequence of; [methylphenidate-IR] – Atomoxetine – Dexamfetamine – no treatment, was cost effective compared to other sequences of drugs for treating ADHD in children (ICER: £485 compared to no treatment). This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that for treating ADHD in children:
 - In stimulant naïve patients, a sequence of atomoxetine – IR-MPH (or XR-MPH) – IR-DEX – no treatment was cost effective compared to the same sequence without atomoxetine (ICER: £15,244 if IR-MPH and £13,241 with XR-MPH)
 - In stimulant contraindicated (naïve) patients, a sequence of atomoxetine – no treatment was cost effective compared to no treatment alone (ICER: £11,523)

This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that for treating ADHD in children:
 - In stimulant naïve patients, a sequence of atomoxetine – IR-MPH – no treatment was not cost effective compared to a sequence of IR-MPH – atomoxetine – no treatment (ICER: £31,007)
 - In stimulant naïve patients, a sequence of atomoxetine – XR-MPH – no treatment was cost effective compared to a sequence of IR-MPH – atomoxetine – no treatment at a threshold of £30,000 per QALY gained, but was not cost effective at a threshold of £20,000 per QALY gained (ICER: £21,971)
 - In stimulant naïve patients with contraindications, atomoxetine was cost effective compared to no treatment at a threshold of £30,000 per QALY gained, but was not cost effective at a threshold of £20,000 per QALY gained (ICER: £21,079)

This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that Lisdexamfetamine was dominant compared to atomoxetine and ER-MPH for treating ADHD in adults. This analysis was assessed as directly applicable with potentially serious limitations.

1.2 Review question: What is the most clinically and cost-effective sequence of pharmacological treatment for children and young people and adults with ADHD?

1.2.1 PICO table

For full details see the review protocol in appendix A.

Table 57: PICO characteristics of review question

Population	Children and young people and adults with ADHD who have previously received medication for ADHD to which they are either intolerant or non-responsive
	Stratify by: <ul style="list-style-type: none">• Age: pre-school children (under 5 years old), children and young people (5-18 years), adults (over 18 years)• Reason previous medication is unsuitable (non-response; intolerance; mixed population or unclear)• The drug(s) previously received

Intervention(s)	<p>The following treatments (all doses), received for a minimum of 2-weeks:</p> <ul style="list-style-type: none"> • CNS stimulants <ul style="list-style-type: none"> ○ methylphenidate ○ methylphenidate modified release ○ dexamphetamine ○ lisdexamfetamine dimesylate • atomoxetine • guanfacine • clonidine • Antidepressants (all drugs should be included separately and not pooled) except for class comparisons in the following groups: <ul style="list-style-type: none"> ○ Tricyclics ○ SSRIs ○ SNRIs ○ MAOIs • Antipsychotics <ul style="list-style-type: none"> ○ Risperidone ○ Olanzapine ○ Clozapine ○ Haloperidol ○ Quetiapine ○ Aripiprazole • Mood stabilisers <ul style="list-style-type: none"> ○ Carbamazepine ○ Valproate ○ Lamotrigine ○ Lithium ○ asenapine • buspirone • bupropion • nicotine • modafinil • melatonin • sativex • anti-cholinesterase inhibitors (ACEi) • Drugs used to treat Parkinson's disease <p>Combinations of the above (including where a medication is added to the previous medication(s))</p>
Comparison(s)	<ul style="list-style-type: none"> • Placebo • Compared against each other • Class vs. class comparisons for stimulants (methylphenidate short- and long-acting together; dexamphetamine and lisdexamfetamine) and SSRIs will also be included
Outcomes	<p>All outcomes to be measured at a short term (up to 3-months) and long-term (beyond 3 months) timepoints. Where multiple timepoints are reported within each definition, the longest timepoint only will be extracted.</p> <p>Critical</p> <ul style="list-style-type: none"> • Quality of life [continuous]

	<ul style="list-style-type: none"> • ADHD symptoms (total; parent) [continuous] [children and young people] • ADHD symptoms (total; teacher) [continuous] [children and young people] • ADHD symptoms (total; self-rated in children 13-18 years and adults) [continuous] • ADHD symptoms (total; carer/partner) [continuous] [adults] • ADHD symptoms (total; investigator) [continuous] • ADHD symptoms (inattention; parent) [continuous] [children and young people] • ADHD symptoms (inattention; teacher) [continuous] [children and young people] • ADHD symptoms (inattention; self-rated in children 13-18 years and adults) [continuous] • ADHD symptoms (inattention; carer/partner) [continuous] [adults] • ADHD symptoms (inattention; investigator) [continuous] • ADHD symptoms (hyperactivity; parent) [continuous] [children and young people] • ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people] • ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous] • ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults] • ADHD symptoms (hyperactivity; investigator) [continuous] • Clinical Global Impressions scale (improved or much improved) [dichotomous] <p>Important</p> <ul style="list-style-type: none"> • Serious adverse events (all) [dichotomous] • Behavioural (children)/Functional (adults) measures [continuous] • Emotional dysregulation [continuous] • Academic outcomes (children) [continuous] • Substance use (alcohol and drug use) [dichotomous] • Self-harm [dichotomous]
Study design	RCTs, systematic reviews of RCTs

1 1.2.2 Methods and process

2 This evidence review was developed using the methods and process described in
3 Developing NICE guidelines: the manual.⁴⁷³ Methods specific to this review question are
4 described in the review protocol in appendix A.

5 This review sought to evaluate the clinical and cost effectiveness of the sequence of
6 pharmacological interventions to treat ADHD in people who have previously been either
7 intolerant or non-responsive to pharmacological treatment. Studies were only included if the
8 population had been selected based on previous failed attempt to use any one specific drug
9 (for example all were intolerant to atomoxetine), an exception was made if the population had
10 all failed a previous attempt of the stimulant class. It was noted in each outcome whether the
11 previous treatment was stopped or continued throughout the trial. Previous treatment
12 continued was termed augmentation and previous treatment that was stopped was called
13 substitution.

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

1 1.2.3 Clinical evidence

2 1.2.3.1 Included studies (pre-school children: under 5 years of age)

3 No relevant clinical studies were identified.

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

6 1.2.3.2 Included studies (children and young people aged 5 to 18)

7 Six randomised trials across 9 papers were included in the review;^{139,197,206,207,256,348,377,469}
8 ⁶⁹⁰ these are summarised in **Table 58** below. Evidence from these studies is summarised in
9 the clinical evidence summary tables below (**Table 60, Table 61: Lisdexamfetamine**
10 **dimesylate versus placebo for ADHD in Children and Young People (substitution for**
11 **methylphenidate)**)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with Control
Clinical response: \geq 30% reduction in ADHD-RS-IV total score AND CGI-I of 1 or 2	26 (1 study) 4 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 1.84 (0.76 to 4.47)	429 per 1000
Adverse events leading to hospitalisation/death/disability	26 (1 study) 4 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RD 0 (-0.18 to 0.18)	0 events in control arm

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 1 MID or by 2 increments if the confidence interval crossed 2 MIDs

12

13 **Table 62: Lisdexamfetamine dimesylate versus atomoxetine for ADHD in Children and**
14 **Young People (substitution for methylphenidate)**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
				Risk with Control
ADHD total symptoms (investigator rated ADHD-RS-IV, change score, 0-54, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-54.	201 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean ADHD total symptoms (investigator rated ADHD-rs-iv, change score, 0-54, high is poor) in the control groups was 41.9
Hyperactivity/impulsivity (Investigator rated, ADHD-RS-IV, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-27.	201 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the control group was 19.4
Inattention (Investigator	201	MODERATE ¹		The mean inattention (investiga

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects
				Risk with Control
rated, ADHD-RS-IV, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-27.	(1 study) 9 weeks	due to imprecision		rated, ADHD-rs-iv, high is poor) the control groups was 22.5
CGI-S improvement of at least one category. A decreased score is an improvement in ADHD symptoms.	192 (1 study) 9 weeks	MODERATE ¹ due to imprecision	RR 1.09 (1 to 1.2)	866 per 1000
Discontinued treatment due to adverse event	262 (1 study) 9 weeks	LOW ¹ due to imprecision	RR 0.84 (0.34 to 2.05)	75 per 1000
Adverse events leading to hospitalisation/death/disability (serious TEAEs)	262 (1 study) 9 weeks	LOW ¹ due to imprecision	RD 0 (-0.01 to 0.01)	0 events in control arm
Function/behaviour (Parent rated, WFIRS-P, 0-3, high is poor) A decreased score is an improvement in ADHD symptoms. 50 items scored 0-3 each.	220 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean function/behaviour (parent rated, wfirs-p, 0-3, high poor) in the control groups was 0.59

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval

1
2 **Table 63, Table 64, Table 66, Table 61, Table 65, Table 62, Table 67).**

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

5 The study results were not meta-analysed as the sequence of treatments in each study was
6 different.

7 **1.2.3.3 Excluded studies**

8 See the excluded studies list in appendix I.

9 **1.2.3.4 Summary of clinical studies included in the evidence review**

10 **Table 58: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Carlson 2007 ¹³⁹	Methylphenidate (n=9) versus placebo (n=8). Treatment augmentation: atomoxetine continued.	Children (6-12 years old) with ADHD not responding to atomoxetine (n=17). Mean age: 9.6 years old.	<ul style="list-style-type: none"> Adverse events leading to hospitalisation/death/disability Discontinuation of treatment due to adverse events 	All patients had insufficient response to an adequate stimulant trial. A sufficient response was a rating of 1 or 2 (very much improved or much improved)

Study	Intervention and comparison	Population	Outcomes	Comments
				on the CGI-I scale. Mean atomoxetine dose at endpoint was 1.07 mg/kg for methylphenidate group and 1.09 mg/kg for placebo group. Mean methylphenidate dose at endpoint was 1.02 mg/kg.
Cutler 2014, Wilens 2012 ^{197,690}	Guanfacine AM (n=154) or guanfacine PM (n=153) versus placebo (n=154) Treatment augmentation: CNS stimulant continued.	Children (6 to 17 years old) with ADHD who are taking CNS stimulants (mixed amphetamine salts, lisdexamfetamine dimesylate, methylphenidate, dexamethylphenidate) but have a partial or suboptimal response (n=461). Mean age: 10.8 years old.	<ul style="list-style-type: none"> • Clinical Global Impressions Improvement • ADHD severity • Discontinuation of treatment due to adverse events 	Considered indirect evidence because patients were required to have exhibited partial (but suboptimal) response to CNS stimulant treatment. This was defined as improvement in, yet persistence of, mild to moderate ADHD symptoms (ADHD - RS-IV total score >24 and CGI > 3) as well as investigator judgement. Mean optimal dose of guanfacine was 0.088 mg/kg/day.
Dittmann 2014, Dittmann 2013, Nagy 2015 ^{206,207,469}	Lisdexamfetamine dimesylate (n=133) versus atomoxetine (n=134) Treatment substitution: methylphenidate stopped.	Children (6-17 years old) with ADHD who had an inadequate response to previous methylphenidate treatment (n=267). Mean age: 10.6 years old.	<ul style="list-style-type: none"> • Clinical Global Impressions Improvement • ADHD symptoms • ADHD symptom subscores • Adverse events leading to hospitalisation/death/disability • Discontinuation of treatment due to adverse events • Weiss Functional Impairment Rating Scale 	Patients were excluded if they experienced intolerable side effects with MPH or failed to respond to more than one course of MPH. Inadequate response defined as: included but not limited to presence of residual ADHD symptoms, inadequate duration of action, variable symptom control, investigators judgement that person might benefit from alternative to methylphenidate. Mean optimal dose at week 4: Lisdexamfetamine: 52.5 mg/day Atomoxetine: 40.2

Study	Intervention and comparison	Population	Outcomes	Comments
				mg/day.
Gadow 2014 ²⁵⁶	Risperidone (and parent training) (n=84) versus placebo (and parent training) (n=84) Treatment augmentation: methylphenidate continued.	Children (6-12 years old) with ADHD and evidence of physical aggression who are taking OROS methylphenidate and do not show sufficient clinical response (n=168). Mean age: 8.9 years old.	<ul style="list-style-type: none"> ADHD severity ADHD severity subscores Behavioural measures (ODD severity, peer conflict scale, CD severity) 	<p>An alternative to OROS methylphenidate was offered to those unable to tolerate medication or swallow pills.</p> <p>An optimal therapeutic response was defined as CGI-I of 1 and parent rated Nisonger Child Behavior Rating Form <15. An sufficient clinical response does not meet that standard.</p> <p>Week 9 dose: Methylphenidate: 46 mg/day for the risperidone group and 45 mg/day for the placebo group. Risperidone: 1.7 mg/day Placebo: 1.9 mg/day</p>
Jain 2011 ³⁴⁸	Lisdexamfetamine dimesylate (n=19) versus placebo (n=7) Treatment substitution: methylphenidate stopped.	Children (6-12 years old) with ADHD who had not responded to previous methylphenidate treatment (n=26). Mean age: 9.	<ul style="list-style-type: none"> Clinical response via ADHD-RS-IV and CGI-I Adverse events leading to hospitalisation/ death/disability 	<p>Non-response to methylphenidate was an ADHD-RS-IV score of ≥ 18 while receiving treatment.</p> <p>Varied fixed dose of lisdexamfetamine from 30 mg/day to 70 mg/day depending on randomisation.</p>
Kollins 2011 ³⁷⁷	Clonidine (n=102) versus placebo (n=96) Treatment augmentation: stimulants continued.	Children aged 6-17 years old with hyperactive or combined ADHD subtype and insufficient response to stimulant treatment (n=198). Mean age: 10.5.	<ul style="list-style-type: none"> ADHD severity ADHD severity subscores Discontinuation of treatment due to adverse events 	<p>Insufficient response defined to be a total ADHD-RS-IV score of ≥ 26.</p> <p>Mean dose of clonidine was 0.3 mg/day in weeks 4 and 5.</p>

1 See appendix D for full evidence tables.

2 1.2.3.5 Included studies (adults)

3 One study was included in the review; ¹³⁴ this is summarised in **Table 59** below.
4 Evidence from these studies is summarised in the clinical evidence summary below (**Table**
5 **67**).

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

3 The study compared guanfacine to placebo in people who had a sub-optimal response to
4 CNS stimulants including lisdexamfetamine, amphetamine/dextroamphetamine or
5 methylphenidate.

6 **Table 59: Summary of studies included in the review**

Study	Intervention and comparison	Population	Outcomes	Comments
Butterfield 2016 ¹³⁴	Guanfacine (n=13) versus placebo (n=13) Treatment augmentation: CNS stimulants continued.	Adults with ADHD who had a sub-optimal response to CNS stimulants (lisdexamfetamine, amphetamine/dextroamphetamine or methylphenidate) (n=26). Mean age: 37.5.	<ul style="list-style-type: none"> • ADHD symptoms • Adverse events leading to hospitalisation/death/disability 	Suboptimal response was defined as participant's dissatisfaction with clinical progress and either an ADHD-RS-IV of ≥ 28 or CGI-S ≥ 4 . Mean final dispensed dose was 4.8 mg/day. Range of 2 to 6 mg/day.

7

1.2.3.6 Quality assessment of clinical studies included in the evidence review

1.2.3.6.1 Clinical evidence (children under 5)

No evidence was found.

1.2.3.6.2 Clinical evidence (children and young people aged 5 to 18)

Table 60: Clinical evidence summary: Methylphenidate versus placebo for ADHD in children and young people (augmentation of atomoxetine)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Methylphenidate versus placebo (95% CI)
Discontinued treatment due to adverse events	21 (1 study) 6 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 1.33 (0.1 to 18.57)	83 per 1000	28 more per 1000 (from 75 fewer to 1000 more)
Adverse events leading to hospitalisation/death/disability	17 (1 study) 6 weeks	VERY LOW ^{a,c} due to risk of bias, imprecision	RD 0 (-0.2 to 0.2)	0 events in control arm	0 fewer per 1000 (from 202 fewer to 202 more)

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 majority of the evidence included an indirect population or 2 increments if the majority of the evidence included a very indirect population
 3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 61: Lisdexamfetamine dimesylate versus placebo for ADHD in Children and Young People (substitution for methylphenidate)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine dimesylate versus placebo (95% CI)
Clinical response: >= 30% reduction in ADHD-RS-IV total score AND CGI-I of 1 or 2	26 (1 study)	VERY LOW ^{1,2}	RR 1.84 (0.76 to	429 per 1000	360 more per 1000 (from 103 fewer to 1000 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine dimesylate versus placebo (95% CI)
	4 weeks	due to risk of bias, imprecision	4.47)		
Adverse events leading to hospitalisation/death/disability	26 (1 study) 4 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RD 0 (-0.18 to 0.18)	0 events in control arm	0 fewer per 1000 (from 181 fewer to 181 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs</p>					

Table 62: Lisdexamfetamine dimesylate versus atomoxetine for ADHD in Children and Young People (substitution for methylphenidate)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine dimesylate versus atomoxetine (95% CI)
ADHD total symptoms (investigator rated ADHD-RS-IV, change score, 0-54, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-54.	201 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean ADHD total symptoms (investigator rated ADHD-rs-iv, change score, 0-54, high is poor) in the control groups was 41.9	The mean ADHD total symptoms (investigator rated ADHD-rs-iv, change score, 0-54, high is poor) in the intervention groups was 6.90 lower (10.32 to 3.48 lower)
Hyperactivity/impulsivity (Investigator rated, ADHD-RS-IV, high is poor) A decreased score is an	201 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the control groups was	The mean hyperactivity/impulsivity (investigator rated, ADHD-rs-iv, high is poor) in the intervention groups was 0.63 standard deviations lower

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lisdexamfetamine dimesylate versus atomoxetine (95% CI)
improvement in ADHD symptoms. Range 0-27.				19.4	(0.91 to 0.35 lower)
Inattention (Investigator rated, ADHD-RS-IV, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-27.	201 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean inattention (investigator rated, ADHD-rs-iv, high is poor) in the control groups was 22.5	The mean inattention (investigator rated, ADHD-rs-iv, high is poor) in the intervention groups was 0.62 standard deviations lower (0.91 to 0.34 lower)
CGI-S improvement of at least one category. A decreased score is an improvement in ADHD symptoms.	192 (1 study) 9 weeks	MODERATE ¹ due to imprecision	RR 1.09 (1 to 1.2)	866 per 1000	78 more per 1000 (from 0 more to 173 more)
Discontinued treatment due to adverse event	262 (1 study) 9 weeks	LOW ¹ due to imprecision	RR 0.84 (0.34 to 2.05)	75 per 1000	12 fewer per 1000 (from 49 fewer to 78 more)
Adverse events leading to hospitalisation/death/disability (serious TEAEs)	262 (1 study) 9 weeks	LOW ¹ due to imprecision	RD 0 (-0.01 to 0.01)	0 events in control arm	0 fewer per 1000 (from 15 fewer to 15 more)
Function/behaviour (Parent rated, WFIRS-P, 0-3, high is poor) A decreased score is an improvement in ADHD symptoms. 50 items scored 0-3 each.	220 (1 study) 9 weeks	MODERATE ¹ due to imprecision		The mean function/behaviour (parent rated, wfirs-p, 0-3, high is poor) in the control groups was 0.59	The mean function/behaviour (parent rated, wfirs-p, 0-3, high is poor) in the intervention groups was 0.08 lower (0.17 lower to 0.01 higher)
1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 63: Guanfacine AM versus placebo for ADHD in children and young people (augmentation of CNS stimulants)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine AM versus placebo (95% CI)
CGI-I (number of people rated as minimally improved or much improved or very much improved, i.e. a score of 1-3)	300 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness and imprecision	RR 1.28 (1.09 to 1.51)	579 per 1000	162 more per 1000 (from 52 more to 295 more)
Early discontinuation of treatment due to adverse events	303 (1 study) 9 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 4.08 (0.46 to 36.08)	7 per 1000	20 more per 1000 (from 4 fewer to 229 more)
Adverse events leading to hospitalisation/death/disability (severe TEAEs)	303 (1 study) 9 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 3.06 (0.32 to 29.09)	7 per 1000	13 more per 1000 (from 4 fewer to 184 more)
ADHD symptoms (ADHD-RS-IV inattention subscale) A decreased score is an improvement in ADHD symptoms. Range 0-27.	303 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision			The mean ADHD-RS-IV inattention subscale reduction groups was 0.36 lower standard deviations lower (0.59 to 0.13 lower)
ADHD symptoms (ADHD-RS-IV) A decreased score is an improvement in ADHD symptoms. Range 0-54.	303 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias,		The mean ADHD-RS-IV: placebo adjusted LS mean reduction in the control groups was	The mean ADHD-RS-IV reduction in the intervention groups was 0.337 lower standard deviations lower (0.56 to 0.11 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine AM versus placebo (95% CI)
		indirectness, imprecision		37.7	
ADHD symptoms (ADHD-RS-IV hyperactivity/impulsivity subscale) A decreased score is an improvement in ADHD symptoms. Range 0-27	303 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision			The mean ADHD-RS-IV hyperactivity/impulsivity subscale reduction was 0.36 lower standard deviations lower (0.59 to 0.14 lower)
<p>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</p> <p>2 Downgraded by 1 increment if the majority of the evidence included an indirect population or 2 increments if the majority of the evidence included a very indirect population</p> <p>3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs</p>					

Table 64: Guanfacine PM versus placebo for ADHD in children and young people (augmentation of CNS stimulants)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine PM versus placebo (95% CI)
CGI-I (number of people rated as minimally improved or much improved or very much improved, i.e. a score of 1-3)	301 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 1.22 (1.03 to 1.44)	579 per 1000	127 more per 1000 (from 17 more to 255 more)
Early discontinuation of treatment due to adverse events	305 (1 study) 9 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 6.04 (0.74 to 49.57)	7 per 1000	33 more per 1000 (from 2 fewer to 317 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Guanfacine PM versus placebo (95% CI)
Adverse events leading to hospitalisation/death/disability (severe TEAEs)	305 (1 study) 9 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 10.07 (1.3 to 77.67)	7 per 1000	59 more per 1000 (from 2 more to 501 more)
ADHD symptoms (ADHD-RS-IV inattention subscale) A decreased score is an improvement in ADHD symptoms. Range 0-27.	305 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision			The mean ADHD-RS-IV inattention subscale reduction was 0.46 lower standard deviations lower (0.69 to 0.24 lower)
ADHD symptoms (ADHD-RS-IV) A decreased score is an improvement in ADHD symptoms. Range 0-54.	305 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision			The mean ADHD-RS-IV reduction was 0.40 lower standard deviations lower (0.62 to 0.17 lower)
ADHD symptoms (ADHD-RS-IV hyperactivity/impulsivity subscale) A decreased score is an improvement in ADHD symptoms. Range 0-27.	305 (1 study) 8 weeks	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision			The mean ADHD-RS-IV hyperactivity/impulsivity subscale: placebo adjusted IS mean reduction was 0.40 lower standard deviations lower (0.62 to 0.17 lower)
<p>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</p> <p>2 Downgraded by 1 increment if the majority of the evidence included an indirect population or 2 increments if the majority of the evidence included a very indirect population</p> <p>3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs</p>					

Table 65: Clonidine versus placebo for ADHD in Children and Young People (augmentation of CNS stimulants)

Outcomes	No of	Quality of	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Clonidine versus placebo (95% CI)
ADHD total symptoms (ADHD-RS-IV improvement, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-54.	197 (1 study)	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD total symptoms (ADHD-rs-iv improvement, high is poor) in the control groups was 39	The mean ADHD total symptoms (ADHD-rs-iv improvement, high is poor) in the intervention groups was 4.20 lower (7.62 to 0.78 lower)
Inattention (ADHD-RS-IV, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-27	197 (1 study) 5 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean inattention (ADHD-rs-iv, high is poor) in the control groups was -5.8	The mean inattention (ADHD-rs-iv, high is poor) in the intervention groups was 2.00 lower (3.90 to 0.10 lower)
Hyperactivity/impulsivity (ADHD-RS-IV, high is poor) A decreased score is an improvement in ADHD symptoms. Range 0-27.	197 (1 study) 5 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean hyperactivity/impulsivity (ADHD-rs-iv, high is poor) in the control groups was -5.8	The mean hyperactivity/impulsivity (ADHD-rs-iv, high is poor) in the intervention groups was 2.10 lower (3.92 to 0.28 lower)
Discontinued treatment due to TEAE	198 (1 study) 5 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 0.31 (0.03 to 2.96)	31 per 1000	22 fewer per 1000 (from 30 fewer to 61 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs</p>					

Table 66: Risperidone and parent training versus placebo and parent training for ADHD in children and young people (augmentation of methylphenidate)

Outcomes	No of	Quality of	Relative	Anticipated absolute effects
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	Participants (studies) Follow up	the evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Risperidone versus placebo (95% CI)
ADHD total symptoms (parent rated ADHD-SC4, Severity Score, 0-3, high is poor) 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	137 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean ADHD total symptoms (parent rated ADHD-sc4, severity score, 0-3, high is poor) in the control groups was 1	The mean ADHD total symptoms (parent rated ADHD-sc4, severity score, 0-3, high is poor) in the intervention groups was 0.20 lower (0.4 lower to 0 higher)
ADHD total symptoms (teacher rated ADHD-SC4, Severity Score, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	86 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD total symptoms (teacher rated ADHD-sc4, severity score, 0-3, high is poor) in the control groups was 0.8	The mean ADHD total symptoms (teacher rated ADHD-sc4, severity score, 0-3, high is poor) in the intervention groups was 0.20 lower (0.43 lower to 0.03 higher)
Inattention (parent rated ADHD-SC4 Severity, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	137 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean inattention (parent rated ADHD-sc4 severity, 0-3, high is poor) in the control groups was 1.1	The mean inattention (parent rated ADHD-sc4 severity, 0-3, high is poor) in the intervention groups was 0.20 lower (0.42 lower to 0.02 higher)
Inattention (teacher rated ADHD-SC4 Severity, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response	86 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean inattention (teacher rated ADHD-sc4 severity, 0-3, high is poor) in the control groups was 1	The mean inattention (teacher rated ADHD-sc4 severity, 0-3, high is poor) in the intervention groups was 0.20 lower (0.47 lower to 0.07 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus placebo (95% CI)
measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.					
Hyperactivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	137 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean hyperactivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was 0.8	The mean hyperactivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the intervention groups was 0.20 lower (0.44 lower to 0.04 higher)
Hyperactivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	86 (1 study) 6 weeks	LOW ^{1,2} due to risk of bias, imprecision		The mean hyperactivity (teacher rated ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was 0.4	The mean item rating ADHD-SC4 severity subscore: hyperactivity (teacher rating) in the intervention groups was 0.10 standard deviations higher (0.14 lower to 0.34 higher)
Impulsivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	137 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean impulsivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was 0.8	The mean impulsivity (parent rated ADHD-sc4 severity subscore, 0-3, high is poor) in the intervention groups was 0.30 lower (0.57 to 0.03 lower)
Impulsivity (teacher rated	86	LOW ^{1,2}		The mean impulsivity (teacher rated	The mean impulsivity (teacher rated

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus placebo (95% CI)
ADHD-SC4 Severity Subscore, 0-3, high is poor) ADHD-SC4 is a 40 item treatment response measure that includes DSM-IV scales of ADHD and ODD and the peer conflict scale.	(1 study) 6 weeks	due to risk of bias, imprecision		ADHD-sc4 severity subscore, 0-3, high is poor) in the control groups was 0.7	ADHD-sc4 severity subscore, 0-3, high is poor) in the intervention groups was 0.20 lower (0.50 lower to 0.10 higher)
Function/behaviour (parent rated ODD DSM-IV, 0-3, high is poor)	137 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean function/behaviour (parent rated odd dsm-iv, 0-3, high is poor) in the control groups was 1.1	The mean function/behaviour (parent rated odd dsm-iv, 0-3, high is poor) in the intervention groups was 0.30 lower (0.54 to 0.06 lower)
Function/behaviour (teacher rated ODD DSM-IV, 0-3, high is poor)	86 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean function/behaviour (teacher rated odd dsm-iv, 0-3, high is poor) in the control groups was 0.4	The mean function/behaviour (teacher rated odd dsm-iv, 0-3, high is poor) in the intervention groups was 0 standard deviations higher (0.26 lower to 0.26 higher)
Function/behaviour (parent rated Peer Conflict Scale, 0-3, high is poor)	137 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean function/behaviour (parent rated peer conflict scale, 0-3, high is poor) in the control groups was 0.6	The mean function/behaviour (parent rated peer conflict scale, 0-3, high is poor) in the intervention groups was 0.30 lower (0.49 to 0.11 lower)
Function/behaviour (teacher rated Peer Conflict Scale, 0-3, high is poor)	86 (1 study) 6 weeks	MODERATE ² due to risk of bias		The mean function/behaviour (teacher rated peer conflict scale, 0-3, high is poor) in the control groups was 0.2	The mean function/behaviour (teacher rated peer conflict scale, 0-3, high is poor) in the intervention groups was 0 higher (0.15 lower to 0.15 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Risperidone versus placebo (95% CI)
Function/behaviour (parent rated CD DSM-IV, 0-3, high is poor)	150 (1 study) 6 weeks	MODERATE ¹ due to imprecision		The mean function/behaviour (parent rated cd dsm-iv, 0-3, high is poor) in the control groups was 0.2	The mean function/behaviour (parent rated cd dsm-iv, 0-3, high is poor) in the intervention groups was 0.10 lower (0.16 to 0.04 lower)
Function/behaviour (teacher rated CD DSM-IV, 0-3, high is poor)	69 (1 study) 6 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean function/behaviour (teacher rated cd dsm-iv, 0-3, high is poor) in the control groups was 0.1	The mean function/behaviour (teacher rated cd dsm-iv, 0-3, high is poor) in the intervention groups was 0 higher (0.12 lower to 0.12 higher)

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
2 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

See appendix F for full GRADE tables.

2.3.6.3 Clinical evidence (adults)

Table 67: Clinical evidence summary: guanfacine versus placebo in adults with a sub-optimal response to CNS stimulants (augmentation of CNS stimulants)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo (while taking amphetamine treatment)	Risk difference with Guanfacine (95% CI)
ADHD total symptoms (ADHD-RS, 0-54, high is poor) Participants returned to study site for evaluation of ADHD symptoms	26 (1 study) 10 weeks	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean ADHD total symptoms (ADHD-rs, 0-54, high is poor) in the control groups was 10.92	The mean ADHD total symptoms (ADHD-rs, 0-54, high is poor) in the intervention groups was 0.93 higher (5.44 lower to 7.3 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo (while taking amphetamine treatment)	Risk difference with Guanfacine (95% CI)
CGI-S (change score, 0-7) Participants returned to study site for evaluation of ADHD symptoms	26 (1 study)	VERY LOW ^{1,2} due to risk of bias, imprecision		The mean cgi-s (change score, 0-7) in the control groups was 1	The mean cgi-s (change score, 0-7) in the intervention groups was 0.15 lower (0.75 lower to 0.45 higher)
Adverse events leading to hospitalisation/death/disabilities	26 (1 study) 10 weeks	LOW ^{1,2} due to risk of bias	RD 0 (-0.14 to 0.14)	0 events in control arm	0 fewer per 1000 (from 138 fewer to 138 more)
<p>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</p> <p>2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.</p>					

1 **1.2.4 Economic evidence**

2 **1.2.4.1 Included studies**

3 **1.2.4.1.1 2008 guideline literature**

4 No studies were identified with the relevant comparison for this review.

5 **1.2.4.1.2 Published literature**

6 Seven health economic studies were identified with the relevant comparison and have been
7 included in this review.^{188, 331, 221, 643, 556, 394, 715} These are summarised in the health economic
8 evidence profiles below (**Table 68, Table 69, Table 70, Table 71**) and the health economic
9 evidence tables in appendix H.

10 Two of these studies compare an atomoxetine treatment algorithm with standard care or no
11 treatment in subgroups of children with ADHD who have either failed stimulants, or are
12 averse or contraindicated to them, in keeping with the populations of this sequencing review.
13 Hong 2009³³¹ is a different version of Cottrell 2008¹⁸⁸ model but is felt to be sufficiently
14 different and is presented as a separate study. Subgroups from these studies that were
15 stimulant naïve are reported in the pharmacological effectiveness review.

16 Three studies compare types of extended release methylphenidate with immediate release
17 methylphenidate in children who are responding sub-optimally to immediate release
18 methylphenidate because of inadequate medication intake. Van der Schans 2015⁶⁴³ and
19 Schawo 2015⁵⁵⁶ are different versions of the Faber 2008²²¹ model but are felt to be
20 sufficiently different and are presented as separate studies.

21 Lachaine 2016³⁹⁴ compares guanfacine extended release added as an adjunct to long-acting
22 stimulants with long-acting stimulants alone in children who are only partially responding to
23 the stimulants.

24 Finally Zimovetz 2016⁷¹⁵ compares Lisdexamfetamine with Atomoxetine in children who had
25 an inadequate response to Methylphenidate.

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

27 **1.2.4.2 Excluded studies**

28 No health economic studies that were relevant to this question were excluded due to
29 assessment of limited applicability or methodological limitations.

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

31

1 **1.2.5 Summary of studies included in the economic evidence review**

2 **Table 68: Health economic evidence profile: [Atomoxetine algorithm versus standard treatment algorithm, or no treatment]**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Cottrell 2008 ¹⁸⁸ (UK)	Partially applicable ^(a)	Potentially serious limitations ^(b)	<p>Markov model of 1 year time horizon with monthly cycles, in children with ADHD. Health states are based on response to treatment and adverse events. How response was defined in the trials is not reported. Based on various RCT evidence. Some of which excluded from the clinical review. Models different sequences and patients move to the next treatment if they fail the current one.</p> <p>3 out of the 5 subgroups evaluated are included in this review question as they are groups who are either failed, averse, or contraindicated to stimulants:</p> <p>Subgroup 1: Stimulant failed patients; Treatment algorithm of atomoxetine → IR-DEX → no treatment. Comparator is the same sequence without</p>	<p>Subgroup 1: £448.78</p> <p>Subgroup 2 (a) (includes IR-MPH): £373.79</p> <p>Subgroup 2 (b) (includes XR-MPH): £256.3</p> <p>Subgroup 3: £395.98</p>	<p>Subgroup 1: 0.03</p> <p>Subgroup 2 (a) (includes IR-MPH): 0.0235</p> <p>Subgroup 2 (b) (includes XR-MPH): 0.0181</p> <p>Subgroup 3: 0.0320</p>	<p>Subgroup 1: £14,945</p> <p>Subgroup 2 (a) (includes IR-MPH): £15,878</p> <p>Subgroup 2 (b) (includes XR-MPH): £14,169</p> <p>Subgroup 3: £12,370</p>	<p>Uncertainty around the ICER not reported.</p> <p>Paper states a probabilistic analysis was done but data on this is not reported.</p> <p>Multiple sensitivity analyses are stated as being undertaken however results are not reported.</p> <p>Model most sensitive to the utility values used.</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			<p>atomoxetine</p> <p>Subgroup 2a: Stimulant averse (exposed) patients; Treatment algorithm of atomoxetine →IR-MPH→IR-DEX→no treatment. Comparator is the same sequence without atomoxetine</p> <p>Subgroup 2b: same as above except IR-MPH is replaced with XR-MPH.</p> <p>Subgroup 3: Stimulant contraindicated (exposed) patients; Atomoxetine followed by no treatment if that fails, compared to no treatment alone.</p>				
Hong 2009 ³³¹ (Spain)	Partially applicable ^(c)	Potentially serious limitations ^(d)	<p>Markov model in children with ADHD, with 1 year time horizon with monthly cycles. Health states are based on response to treatment and adverse events. How response was defined in the trials is not reported. Based on various RCT evidence. Some of which excluded from the clinical review. Models different sequences and patients move to the next treatment if they fail the current one.</p>	£831 (e)	0.039	£21,528	<p>Uncertainty around the ICER not reported.</p> <p>Paper states a probabilistic analysis was done but data on this is not reported.</p> <p>Multiple sensitivity analyses are stated as being undertaken however results are not reported.</p> <p>Model most sensitive to the utility values used.</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			<p>1 out of the 3 subgroups evaluated are included in this review question as it is a group that have been previously exposed to stimulants and failed:</p> <p>Stimulant failed patients: Atomoxetine compared to no treatment.</p>				

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial, IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine

(f) UK study with an NHS cost perspective. However; population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.

(g) Potential conflict of interest. Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. Based on some data that has been excluded for this question. No adverse event costs or other resource use costs included.

(h) Non UK. Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.

(i) Potential conflict of interest. Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. No adverse event costs or other resource use costs included. Based on some data that has been excluded for this question.

(j) 2008 Spanish Euros converted to GBP using purchasing power parities.

Table 69: Health economic evidence profile: [Extended release methylphenidate versus Immediate release methylphenidate]

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Faber 2008 ²²¹ (Netherlands)	Partially applicable ^(a)	Potentially serious limitations ^(b)	<p>Markov model in children with ADHD, with a 10 year time horizon and cycles of one day. The markov model is preceded by a 2 month primary phase. Patients going into the primary phase are youths with sub optimal symptom control from</p>	£1,321 ^(c)	0.13	£10,161	A series of univariate sensitivity analyses were performed on most of the model parameters. This involved varying base case values +/-25%. The parameters that affected the ICER the most were

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			methylphenidate immediate release. Only those who are then responding to immediate release methylphenidate but the treatment is suboptimal due to inefficient exposure (because of the multiple daily administration required) go into the markov phase. Staying on IR MPH is then compared to optimal response with OROS MPH. Treatment effect is based on a combination of assumptions from a panel of experts and some literature. Costs include intervention costs, as well as other healthcare costs such as consultation costs, costs for 'other interventions'. Also includes cost of special education, however as the total costs were broken down with this reported separately; these have been deducted from the incremental costs.				resource use in the optimal and suboptimal states, and the probability of stopping treatment. The cost of OROS methylphenidate also had a big impact on the ICER.
Van Der Schans 2015 ⁶⁴³ (Netherlands)	Partially applicable ^(d)	Potentially serious limitations ^(e)	Markov model in children with ADHD, with 4 states, a 10 year time horizon and cycles of one day. The markov model is preceded by a 2 month primary phase. This 2 month phase was considered the time interval that a patient was	MPH OROS vs MPH IR: £597 ^(f) Medikinet/ Equasym vs MPH IR: -£449	MPH OROS vs MPH IR: 0.318 Medikinet/ Equasym vs MPH IR: 0.318	MPH OROS vs MPH IR: £1,879 Medikinet/ Equasym vs MPH IR: Dominant	A series of univariate sensitivity analyses were performed on most of the model parameters. This involved varying base case values +/-25%. In addition a multivariate sensitivity analysis was

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			<p>identified as a true non-responder or as a potential suboptimal responder but with compliance being the problem. This group of potential responders then went on to be in the markov.</p> <p>Staying on IR MPH is then compared to switching to modified release versions; OROS MPH, or Medikinet CR/Equasym XL.</p> <p>Treatment effect is based on a combination of assumptions from a panel of experts and some literature.</p> <p>Costs include intervention costs, as well as other healthcare costs such as consultation costs, costs for 'other interventions'. It also includes cost of special education, and indirect costs (caregiver costs), however as the total costs were broken down with this reported separately; these have been deducted from the incremental costs.</p>			The Medikinet/ Equasym comparator is dominant overall because it is cheaper than MPH OROS and has the same QALYs.	<p>performed where the worst case parameter values were analysed.</p> <p>The parameter most likely to alter the results was the percentage of patients benefitting from switching from IR MPH to one of the extended release versions.</p>
Schawo 2015 ⁵⁵⁶ (Netherlands)	Partially applicable ^(g)	Very serious limitations ^(h)	Markov model in children with ADHD who are responding sub-optimally because of incorrect medication intake.	-£4,231	0.15 Note that this is the	MPH OROS dominant.	All analyses resulted in cost savings and increased QALYs for MPH OROS, except for when transition

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
			<p>The model has 4 states, and a 12 year time horizon with cycles of 1 day.</p> <p>Staying on IR MPH is then compared to switching to modified release version of OROS MPH. Treatment effect is based on estimates from a panel of experts.</p> <p>Costs include intervention costs, as well as other healthcare costs such as consultation costs, costs for 'other interventions'. It also includes cost of special education, and indirect costs (caregiver costs). Indirect costs were deducted in a sensitivity analysis so the incremental cost from this analysis is the one reported here.</p>		<p>incremental cost reported in the sensitivity analysis that excluded caregiver utility.</p>		<p>rates of OROS were assumed equal to IR MPH. This analysis also resulted in zero incremental QALYs.</p>

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial, IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine

(a) Non UK, uses different but similar discount rates, does not use EQ-5D and utilities not from the public.

(b) Potential conflict of interest. A lot of assumptions/inputs from a panel of experts and limited data.

(c) 2005 Dutch Euros reported as 2005 UK pounds. Total costs in the study had the special education costs deducted, then these were converted to UK pounds and the incremental cost calculated.

(d) Non UK, uses different discount rates

(e) Potential conflict of interest as one author has received grants from companies that make some of the products. A lot of assumptions/inputs from a panel of experts and limited data.

(f) 2013 Dutch Euros reported as 2013 UK pounds. Total costs in the study had the special education and indirect costs deducted, then these were converted to UK pounds and the incremental cost calculated.

(g) Non UK, uses different discount rates

(h) Potential conflict of interest. A lot of assumptions/inputs from a panel of experts and limited data. All transition probabilities are from a Delphi panel of 4 experts, hence this has been given the lowest quality rating of the three studies because there are more assumptions in this study.

Table 70: Health economic evidence profile: [Guanfacine extended release (GXR) + long-acting stimulant versus long-acting stimulant monotherapy]

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Lachaine 2016 ³⁹⁴ (Canada)	Partially applicable ^(a)	Potentially serious limitations ^(b)	<p>Two stage markov model with a 1 year time horizon and weekly cycles. Four health states based on the CGI-S. Looks at a population of children who are partial responders to long acting stimulants and compares staying on long acting stimulants versus adding Guanfacine as an adjunct.</p> <p>Treatment effect based on a single 8 week trial.</p> <p>Effect outcome is QALYs and also patient weeks with a response.</p> <p>Costs include interventions costs and costs in each health state related to managing ADHD.</p>	£373 ^(c)	<p>QALYs = 0.028</p> <p>Patient weeks with a response = 6.57</p>	£13,321	<p>Probabilistic sensitivity analysis done. 95% probability of intervention being cost effective.</p> <p>Several one-way sensitivity analyses were performed by varying a single variable individually within lower and upper bounds of all key parameters.</p> <p>The parameters with the greatest impact on base-case ICER was (i) the calculation of transition probabilities based on trial data for the first 8 weeks and then LOCF for the remainder of the study period and (ii) the initial health state distribution assuming 100 % of patients started in the severe state.</p> <p>In a sensitivity analysis where patients were maintained on treatment and could transition between health states during the</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
							weeks 9-52 period the ICER increased to \$47,909 (almost £27,000).

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; LOCF: last observation carried forward; CGI-S: Clinical Global Impression - Severity

(a) Canadian cost perspective. Uses utilities based on TTO direct elicitation.

(b) Potential conflict of interest; funded by Shire who make Guanfacine. Assumptions about extrapolation of effect. Effectiveness based only on one trial which is only 9 weeks.

(c) 2013 Canadian dollars reported as 2013 UK pounds. Also had a societal perspective where productivity losses were included but as this was reported separately only the ministry of health perspective has been reported here.

Table 71: Health economic evidence profile: [Lisdexamfetamine versus Atomoxetine]

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
Zimovetz 2016 ⁷¹⁵ (UK)	Directly applicable ^(a)	Potentially serious limitations ^(b)	Decision tree model with 1 year time horizon comparing lisdexamfetamine (LDX) to atomoxetine (ATX) in children who had an inadequate response to methylphenidate (MPH). People can either tolerate or not tolerate the treatment, and then those who tolerate can either respond or not respond. Treatment effect based on a single head to head 9 week trial of the two drugs. Includes healthcare resource use of responders and non-responders.	£20	0.011	£1,586	Probabilistic sensitivity analysis done. probability intervention cost effective was 86%. Various one way sensitivity analyses tested as well as two alternative scenarios performed probabilistically using the base case inputs; one using efficacies from the MTC and one using utility weights from the direct trial. For the additional two PSA scenarios; LDX was dominant using the MTC effect estimates, and had

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (QALYs)	Cost-effectiveness	Uncertainty
							<p>an ICER of £4,968 when using the head to head trial utilities.</p> <p>LDX remained cost effective in all sensitivity analyses and was dominant in two of them; assumptions about drug costs, and using MTC effectiveness.</p>

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; MTC; mixed treatment comparison.

(a) UK perspective. EQ-5D.

(a) Potential conflict of interest because of funders. Some structural components that may not reflect reality. Assumptions about extrapolation of effect. Effectiveness based only on one trial which is only 9 weeks and could be argued that effect of comparator may be underestimated. SA uses MTC data but this is again data funded by the manufacturer of the intervention. Potential conflict of interest. A lot of assumptions/inputs from a panel of experts and limited data.

1

2 Subgroup 3 of the Cottrell¹⁸⁸ study, and the subgroup presented from the Hong³³¹ study,
3 have similar interventions (atomoxetine followed by no treatment compared to no treatment,
4 and atomoxetine compared to no treatment, respectively), yet they have quite different
5 ICERS. One reason for this is that the cost of atomoxetine in the Hong study, which is
6 European, is around twice the cost atomoxetine in the Cottrell study, which might explain
7 why the incremental cost in Hong is about twice that of Cottrell. One concern the committee
8 had about the Cottrell and Hong studies was that the studies assumed atomoxetine did not
9 have an insomnia side effect, which the committee believed was an underestimate. Had this
10 been included in the Cottrell study, it may have had some effect on the result, but it is
11 uncertain if it would have such a large effect as to increase the ICER above the NICE
12 threshold.

13 The studies comparing extended release methylphenidate to immediate release
14 methylphenidate all have results showing extended release methylphenidate is cost effective,
15 but they can vary from showing the intervention is dominant to having an ICER of around
16 £10,000. This could be explained by the fact that the Van der Schans and Schawo studies
17 are updating the Faber model and therefore there are some differences between all three
18 studies. Faber for example has different health states for the intervention and comparator
19 arm, whereas Van Der Schans and Schawo do not. In the Faber paper there was no
20 suboptimal state in the comparator arm, instead there was a non-compliance state which had
21 the same costs attached as the optimal state, meaning that there might have been lower
22 costs in the comparator arm in that study leading to a larger incremental cost for
23 consultations and other intervention costs, than in van der Schans. However the incremental
24 medication costs are larger in the Faber model, as MPH OROS is around 5 times more
25 expensive than MPH IR. It is less than 4 times more expensive in the Van der Schans study.
26 Therefore there are many trade-offs taking place affecting the total incremental costs of the
27 studies.

28 The utilities are from different sources in all the papers, and are much closer together in the
29 Faber study, helping to explain why the incremental QALY is smaller in that study.

30 The medication costs are lower for the medikinet/Equasym arm compared to MPH OROS
31 and this alongside the savings from the resource use (because more people are 'optimal'
32 compared to IR MPH) is why there is a cost saving of £449 in the Van Der Schans study.

33 In the Schawo paper, the transition probabilities are very different to Faber and Van Der
34 Schans. Transitions that were not in Faber like restarting treatment after it is stopped are
35 included and this is more so in the OROS arm, so there are higher costs of the other
36 interventions aside from medication in the IR MPH arm which are expensive, and could
37 explain the very large cost saving compared to the other studies. There is not a breakdown
38 of total costs in the Schawo paper which might have provided more detail.

39 **1.2.5.1 Unit costs**

40 Please see section 1.1.4.4 for an illustration of the costs of the different medications.

41 Note that some of the clinical data identified for this question involves adding adjuncts to
42 existing medication rather than changing medication, which would incur higher drug costs.
43

44 **1.2.6 Resource impact**

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

47

1 1.2.7 Evidence statements

2 1.2.7.1 Clinical evidence statements

- 3 • No quality of life data was found for any age group in this evidence report.
- 4 • No clinical evidence was found in the pre-school children age group for any interventions

6 **Methylphenidate versus placebo(augmentation of atomoxetine)**

- 7 • No clinical difference for discontinuation due to adverse events and serious adverse events (1 study very low quality, children and young people).

10 **Lisdexamfetamine versus placebo (augmentation of CNS stimulants)**

- 11 • Clinical benefit of lisdexamfetamine dimesylate for a combined ADHD total, inattention and hyperactivity symptoms and CGI-I outcome (1 study very low quality)
- 12 • No clinical difference was found for adverse events leading to hospitalisation/death/disability (1 study very low quality, children and young people)

16 **Lisdexamfetamine versus atomoxetine (substitution for methylphenidate)**

- 17 • Clinical benefit of lisdexamfetamine compared to atomoxetine for investigator rated ADHD total, hyperactivity and inattention symptoms (1 study low quality)
- 18 • No clinical difference for discontinuation of treatment due to adverse events or adverse events leading to hospitalisation/death/disability (1 study low quality, children and young people), or behavioural outcomes (1 study moderate quality), and CGI-S (1 study moderate quality, children and young people).

24 **Guanfacine versus placebo**

- 25 • Clinical benefit of guanfacine for CGI-I (1 study low quality, children and young people)
- 26 • Clinical harm of methylphenidate in adverse events leading to hospitalisation/death/disability (1 study very low quality, children and young people)
- 27 • No clinical difference for ADHD total, inattention and hyperactivity symptoms (1 study very low quality, adults), CGI-S (1 study very low quality, adults), discontinuation due to adverse events (1 study very low quality, children and young people) and CGI-S and adverse events leading to hospitalisation/death/disabilities (1 study very low to low quality, adults)

34 **Clonidine versus placebo (augmentation of CNS stimulants)**

- 35 • No clinical difference in investigator rated ADHD total, inattention and hyperactivity symptoms and no clinical difference in discontinuing treatment due to adverse events (1 study very low quality, children and young people)

39 **Risperidone and parent training versus placebo (augmentation of methylphenidate)**

- 40 • In children and young people there was a clinical benefit of risperidone for parent rated and teacher rated ADHD total symptoms (1 study moderate to low quality), parent and teacher rated ADHD inattention symptoms (1 study moderate quality), ODD DSM-IV (parent rated, 1 study low quality)
- 41 • In children and young people there was clinical harm of risperidone for teacher and parent rated ADHD hyperactivity symptoms (1 study low to moderate quality)
- 42 • No clinical difference for ADHD inattention symptoms (1 study low quality, children and young people) and teacher rated and parent rated behavioural outcomes (2 studies, moderate to very low quality)

1.2.7.2 Health economic evidence statements

- One cost-utility analysis found that for treating ADHD in children:
 - In stimulant failed patients, a sequence of Atomoxetine followed by IR-DEX followed by no treatment was cost effective compared to the same sequence without atomoxetine (ICER: £14,945)
 - In stimulant averse (exposed) patients, a sequence of atomoxetine followed by IR-MPH (or XR-MPH) followed by IR-DEX followed by no treatment was cost effective compared to the same sequence without atomoxetine (ICER: £15,878 if IR-MPH and £14,169 if XR-MPH)
 - In stimulant contraindicated (exposed) patients, a sequence of Atomoxetine followed by no treatment was cost effective compared to no treatment alone (ICER: £12,370)

This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that Atomoxetine was cost effective compared to no treatment at a threshold of £30,000 per QALY gained for treating ADHD in children who have failed stimulants, but was not cost effective at a threshold of £20,000 per QALY gained (ICER: £21,528). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that OROS MPH was cost effective compared to IR-MPH for treating ADHD in children with sub optimal symptom control from IR-MPH because of incorrect medication intake (ICER: £10,161). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that for treating ADHD in children;
 - OROS MPH was cost effective compared to IR-MPH in children with sub optimal symptom control from IR-MPH because of poor compliance (ICER: £1,879).
 - Medikinet CR/Equasym XL was dominant (less costly and more effective) compared to IR-MPH in children with sub optimal symptom control from IR-MPH because of poor compliance

This analysis was assessed as partially applicable with potentially serious limitations.

- One cost-utility analysis found that OROS MPH was dominant compared to IR-MPH for treating ADHD in children with sub optimal symptom control from IR-MPH because of incorrect medication intake. This analysis was assessed as partially applicable with very serious limitations.
- One cost-utility analysis found that Guanfacine extended release (GXR) + long-acting stimulant was cost effective compared with long-acting stimulant monotherapy for treating ADHD in children who are partial responders to long acting stimulants (ICER: £13,321). This analysis was assessed as partially applicable with potentially serious limitations.
- One-cost-utility analysis found that Lisdexamfetamine was cost effective compared to Atomoxetine for treating ADHD in children who had an inadequate response to methylphenidate (ICER: £1,586). This analysis was assessed as directly applicable with potentially serious limitations.

1.3 Recommendations

Children and young people 5 years¹ and over

¹ At the time of consultation (September 2017), medicines used for the treatment of ADHD did not have a UK marketing authorisation for use in children aged 5 years and under for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- 1 C2. Offer medication for children and young people with ADHD aged 5 years and over if their
2 ADHD symptoms are having a persistent significant impact in at least one domain of
3 their everyday life after environmental modifications.
- 4 C3. Offer methylphenidate as first-line pharmacological treatment for children aged 5 years²
5 and over and young people with ADHD.
- 6 C4. Consider lisdexamfetamine³ for children aged 5 years and over and young people whose
7 ADHD symptoms are not responding adequately to methylphenidate.
- 8 C5. Consider dexamfetamine⁴ for children aged 5 years and over and young people whose
9 ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer
10 effect profile.
- 11 C6. Offer atomoxetine or guanfacine⁵ to children aged 5 years and over and young people if:
12
 - they cannot tolerate methylphenidate or lisdexamfetamine, or
 - their symptoms have not responded to separate 6-week trials of lisdexamfetamine
13 and methylphenidate, having tried alternative formulations and adequate doses.
14

15 **Adults**

- 16 C7. Offer medication to adults with ADHD if their ADHD symptoms are having a significant
17 impact on at least one domain of their everyday life after environmental modifications.
- 18 C8. Consider lisdexamfetamine⁶ as a first line pharmacological treatment for adults with
19 ADHD.
- 20 C9. Consider methylphenidate⁷ for adults whose ADHD symptoms are not responding
21 adequately to lisdexamfetamine.
- 22 C10. Consider dexamfetamine⁸ for adults whose ADHD symptoms are responding to
23 lisdexamfetamine but who cannot tolerate the longer effect profile.

² At the time of consultation (September 2017), methylphenidate did not have a UK marketing authorisation for this indication in children aged 5 years or under. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

³ At the time of consultation (September 2017) lisdexamfetamine did not have a UK marketing authorisation for this indication in children aged 5 years or under. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

⁴ At the time of consultation (September 2017) dexamfetamine was only licensed for the treatment of ADHD in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. Dexamfetamine is not licensed for the treatment of ADHD in children and adolescents aged 5 to 17 years who have responded to, but are intolerant to lisdexamfetamine. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

⁵ At the time of consultation (September 2017) atomoxetine or guanfacine did not have a UK marketing authorisation for this indication in children aged 5 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

⁶ At the time of consultation (September 2017) lisdexamfetamine was licensed for use in adults with symptoms of ADHD that pre-existed in childhood. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

⁷ At the time of consultation (September 2017) methylphenidate did not have a UK marketing authorisation for this indication in adults. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- 1 C11. Offer atomoxetine⁹ to adults if:
- 2 • they cannot tolerate lisdexamfetamine or methylphenidate, or
- 3 • their symptoms have not responded to separate 6-week trials of lisdexamfetamine
- 4 and methylphenidate, having considered alternative formulations and doses.
- 5 **General**
- 6 C12. Obtain a second opinion or refer to tertiary services if ADHD symptoms in a child aged
- 7 5 years or over, a young person or adult are unresponsive to one or more stimulants
- 8 and one non-stimulant.
- 9 C13. Do not offer any medication for ADHD other than in recommendations C1 to C11
- 10 outside a specialist (tertiary) ADHD service (for example, guanfacine¹⁰ for adults,
- 11 clonidine¹¹ for children with ADHD and sleep disturbance, rages or tics).
- 12 C14. Offer the same medication choices to children aged 5 years and over, young people
- 13 and adults with ADHD who have an anxiety disorder, tic disorder or autism spectrum
- 14 disorder as other people with ADHD.
- 15 C15. Do not offer immediate-release stimulants or modified –release stimulants that can be
- 16 easily injected or insufflated if there is a risk of stimulant misuse or diversion.
- 17 C16. Be cautious about prescribing stimulants for ADHD if there is a risk of stimulant
- 18 diversion for cognitive enhancement or appetite suppression.
- 19 C17. For children aged 5 years and over, young people and adults with ADHD experiencing
- 20 an acute psychotic or manic episode:
- 21 • Do not offer any new medication for ADHD and
- 22 • Stop any previously prescribed medication for ADHD.
- 23 C18. Consider an atypical antipsychotic (for example, risperidone¹²) in addition to stimulants
- 24 for children aged 5 years and over, young people and adults with ADHD and co-
- 25 existing pervasive aggression, rages or irritability causing severe impairment and
- 26 inadequately responsive to behavioural interventions.

27 1.3.1 Research recommendations

- 28 RR1. What is the clinical and cost effectiveness of ADHD medications in people with ADHD
- 29 and tic disorders, a history of psychosis or mania or emotional dysregulation?

⁸ At the time of consultation (September 2017) dexamfetamine did not have a UK marketing authorisation for this indication in adults. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

⁹ At the time of consultation (September 2017) atomoxetine was licensed for use in adults with symptoms of ADHD that pre-existed in childhood. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

¹⁰ At the time of consultation (September 2017) guanfacine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

¹¹ At the time of consultation (September 2017) clonidine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

¹² At the time of consultation (September 2017) risperidone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

1 RR2. What is the clinical and cost effectiveness of ADHD medications in people with ADHD
2 who are treatment naive?

3 RR3. What is the clinical and cost effectiveness of various ADHD prescribing strategies when
4 monotherapy has failed?

5 See also the rationales in appendix J.

6 **1.4 Rationale and impact: children under 5**

7 **1.4.1 Why the committee made the recommendations**

8 There was very little evidence identified for drug treatment for children under 5 years with
9 ADHD. Drug treatment is not offered routinely to children under 5 years in current practice
10 and the committee agreed there was not enough evidence to support a change in practice for
11 the under 5 age group.

12 However, the committee agreed that, based on the limited evidence and their clinical
13 experience, drug treatment might be an option for children in this age group with very severe
14 ADHD symptoms and whose symptoms and impairment remain after a parent- training
15 programme but this should only be in the context of a specialist service.

16 **1.4.2 Why we need recommendations on this topic**

17 While the use of stimulants is well established in the treatment of children age 5-18 with
18 ADHD there are unanswered questions for clinicians treating all age groups concerning when
19 to use medication, which medication to use, the best sequence of medications to use, the
20 optimum duration of treatment, when it is appropriate to consider drug discontinuation and
21 which drug treatments to use in the presence of co-occurring conditions.

22 **1.4.3 Impact of the recommendations on practice**

23 The recommendation reflects current practice so the committee agreed there should be no
24 change in practice.

25 **1.5 Rationale and impact: children and young people age 5 -18** 26 **and adults**

27 **1.5.1 Why the committee made the recommendations**

28 Evidence showed a clinically important benefit for monotherapy with the stimulants
29 methylphenidate and lisdexamfetamine compared with placebo or other drugs. This was
30 supported by the committee's experience that stimulants work quicker than non-stimulant
31 drugs (for example, atomoxetine and guanfacine), which can take up to 2 weeks to have an
32 effect. The committee used the evidence, their experience and the drug licensing to
33 recommend methylphenidate as a first treatment for children aged 5 years and over and
34 young people, and lisdexamfetamine as a first treatment for adults.

35 The committee acknowledged the rising cost of dexamfetamine and agreed that it should
36 only be considered when lisdexamfetamine is effective but the longer effect profile is not well
37 tolerated.

38 The committee agreed that if an initial stimulant has not been effective then another should
39 be considered. This would be lisdexamfetamine for children aged 5 years and over and
40 young people, and methylphenidate for adults. The committee acknowledged that these

1 recommendations were outside the licensing indications, but based their decision on the
2 evidence and their clinical experience that stimulants are more effective than non-stimulants.

3 Atomoxetine and guanfacine were the non-stimulant drugs with the most convincing
4 evidence. The committee noted that atomoxetine is more widely used and that there was
5 stronger evidence for a benefit of atomoxetine compared with placebo than guanfacine
6 compared with placebo. One trial directly comparing atomoxetine with guanfacine generally
7 showed a clinically important benefit of guanfacine. Taking into account the licensing status
8 of these drugs and the familiarity of most healthcare professionals with them, the committee
9 recommended that in children aged 5 years and over and young people either drug could be
10 offered after intolerance or a lack of response to stimulants (methylphenidate and
11 lisdexamfetamine). As guanfacine is not licensed for use in adults and there was no evidence
12 specifically supporting its use in this population, the committee recommended atomoxetine
13 for adults with intolerance or a lack of response to stimulants.

14 There was not enough evidence to justify specific recommendations for other drugs so the
15 committee recommended that after at least one stimulant and non-stimulant had been tried,
16 healthcare professionals should obtain a second opinion or refer to a tertiary service.

17 Medication choice for people with co-existing conditions

18 There was very little evidence on medication choice for people with ADHD and co-existing
19 conditions and so the committee made research recommendations to address this gap. The
20 committee agreed that neither the available evidence nor their experience justified a different
21 choice of ADHD medication for people with ADHD and co-existing conditions, but there
22 should be slower titration, more careful monitoring and recording of side effects, and regular
23 weekly contact. However, the committee recommended that ADHD medication should be
24 stopped in people experiencing a psychotic episode because they agreed that ADHD
25 medication could worsen psychotic symptoms.

26 1.5.2 Why we need recommendations on this topic

27 While the use of stimulants is well established in the treatment of children aged 5-18 with
28 ADHD there are still key unanswered questions for clinicians treating all age groups
29 concerning when to use medication, which medication to use, the best sequence of
30 medications to use, the optimum duration of treatment, when it is appropriate to consider
31 drug discontinuation and which drug treatments to use in the presence of co-occurring
32 conditions.

33 1.5.3 Impact of the recommendations on practice

34 The recommendations reflect good current practice.

35 1.6 The committee's discussion of the evidence for 36 pharmacological efficacy

37 1.6.1 Interpreting the evidence

38 1.6.1.1 The outcomes that matter most

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

1 even if the trials were blinded, parents might have been aware of the drug or placebo status,
2 given the effect profile of some of the stimulant medication used for ADHD.

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

6 **1.6.1.2 The quality of the evidence**

7 The quality of the evidence for this review ranged widely between age groups and individual
8 medications. The majority of the evidence was moderate or low quality for the more
9 commonly prescribed medications (for example methylphenidate, atomoxetine) whereas for
10 the less commonly prescribed medications (for example clonidine, risperidone) the quality of
11 evidence was predominantly low or very low quality.

12 In children under the age of 5 there was very little evidence (only comparisons between
13 methylphenidate and placebo, methylphenidate and risperidone and risperidone and
14 placebo) and the majority of it was low or very low quality. There was a greater breadth of
15 evidence in children aged 5 to 18 and adults although the majority of comparisons were
16 between drugs and placebo, there was little in the way of large or high quality studies directly
17 comparing different drugs.

18 Studies rarely reported quality of life or functional measures but frequently just ADHD
19 symptoms. The committee noted that these were often reported by the people taking the
20 drugs themselves (if adults) or parents who, even if the trials were blinded, might have been
21 aware of the drug or placebo status, given the effect profile of some of the stimulant
22 medication used for ADHD. Some studies did use teacher reports who were less likely to be
23 aware.

24 **1.6.1.3 Benefits and harms**

25 As undertaking a network meta analysis was not possible to combine all the clinical data in
26 any of the age groups (see the methodology chapter for further details), the committee had
27 the difficult task of evaluating the different pairwise comparisons presented to them and
28 trying to draw conclusions on both the direct but also indirect relationships between drug
29 treatments. In terms of the pathway of drugs that were recommended; the committee agreed
30 that stimulants are effective against placebo, and in clinical practice are the most commonly
31 used ADHD treatment and are favoured because of their fast acting nature. Modified release
32 formulations are also available. There are many circumstances to consider when deciding
33 whether a short or long acting formulation of methylphenidate is used. From the experience
34 of the committee; most clinicians would tend to use long acting in school children but may
35 titrate with short acting to assess side effects and often a mix of short and long acting is
36 used. A direct comparison of the two preparations did not show any differences in
37 effectiveness or side effects. A modified release formulation can provide more stability in
38 symptom control throughout the day, and also can help prevent the stigma associated with
39 ADHD compared to if children have to take multiple tablets per day necessitating going to the
40 'office' in front of peers for example. Therefore there may be a wider impact on quality of life
41 than only through control of symptoms. For these reasons the committee stated in the
42 recommendation that stimulants in either formulation can be offered.

43 **1.6.1.3.1 Children under the age of 5**

44 The committee agreed that there was insufficient evidence to justify routine use of
45 medication in this age group. However if ADHD symptoms are very persistently pervasive
46 across all contexts and significant in their impact, referral to a tertiary centre is advised. The
47 ADHD tertiary care specialist may consider medication having carefully reviewed diagnosis
48 and other options. See the combination review and rationale for more information about

1 these recommendations (for more information, see evidence report F on combination
2 treatment).

31.6.1.3.2 **Medication choices for children aged 5 to 18 and adults**

4 The committee noted that the drugs that showed a most convincing clinically important
5 benefit from the evidence in this review were methylphenidate, atomoxetine,
6 lisdexamfetamine, dexamphetamine and guanfacine. Although other drugs (for example
7 venlafaxine, modafinil), showed benefits for some outcomes, they were generally less
8 consistent, less evident in the teacher/investigator rated outcomes prioritised by the
9 committee and supported by smaller, lower quality trials. The committee therefore chose not
10 to specifically recommend the use of any other medication but instead to advise that any
11 other medication should only be considered in the context of specialist ADHD services.

12 The committee noted that stimulant medication generally has a faster onset compared to
13 non-stimulant medication. This means that in terms of first line drug treatment, starting with
14 stimulant medication (methylphenidate, in age 5- 18 and lisdexamfetamine in adults) allows
15 for healthcare professionals to quickly determine if a person is responsive to a first line
16 treatment and move on to other options appropriately. Starting with non-stimulant medication
17 (for example atomoxetine) would result in all people with ADHD undergoing a longer period
18 of titration and waiting to determine if they are responsive to their first medication option.

19 Lisdexamfetamine is a pro-drug of dexamphetamine, and has a longer effect profile. The
20 committee agreed, based on consensus, that the only situation in which they would
21 recommend dexamphetamine would be when the person has responded very well to
22 lisdexamfetamine but is unable to tolerate its longer effect profile.

23 The committee noted that of the non-stimulant medication atomoxetine and guanfacine were
24 the non-stimulant drugs that had the largest and most convincing evidence base
25 demonstrating a clinically important benefit. The committee noted that atomoxetine is more
26 widely used currently and that the evidence showing a benefit of atomoxetine compared to
27 placebo was stronger than that showing a benefit of guanfacine compared to placebo. There
28 outcomes showing a clinically important benefit for guanfacine compared to placebo were
29 generally based on parent ratings as opposed to teacher ratings, unlike atomoxetine. There
30 was one trial directly comparing atomoxetine with guanfacine which generally showed a
31 clinically important benefit of guanfacine compared to atomoxetine.

321.6.1.3.3 **Comorbidities**

33 The committee noted there was no evidence to support deviating from the usual ADHD
34 treatmentADHD pathway in people with ADHD and co-existing conditions (for example,
35 anxiety disorder, tic disorder or autism spectrum disorder). The exceptions were people who
36 misused substances and people who are experiencing an acute psychotic or manic episode.
37 Historically clinicians have been hesitant to use stimulant medication in people with co-
38 existing conditions, such as anxiety disorder, tic disorder and autism spectrum disorder, for
39 fears of worsening their co-existing conditions. However there was no evidence identified in
40 this review or the pharmacological safety review to support this. It was noted there was a
41 dearth of evidence evaluating the impact of ADHD treatments on people with co-morbidities,
42 either the groups were not distinguished within the analysis or these groups had been
43 excluded from the trial. The committee's consensus view was that healthcare professionals
44 should consider the same medication choices for these populations, although they should
45 consider the individual circumstances and have slower dose titration and more frequent
46 monitoring.

47 The committee agreed that prescribing stimulant medication to people with ADHD with a
48 history of/at risk of stimulant misuse or stimulant diversion is challenging. The committee
49 recommended that healthcare professionals are generally cautious about prescribing
50 stimulant medication in this context, although it should not be an absolute contraindication.

1 Healthcare professionals should also consider if less readily abused forms of stimulants (e.g.
2 modified release) or non-stimulant medication (e.g. atomoxetine or guanfacine) may be a
3 better option for these people.

4 The committee discussed, based on their own experience the treatment of people who are
5 currently experiencing an acute psychotic or manic episode. The GC noted that healthcare
6 professionals should not treat ADHD symptoms in someone who is acutely psychotic and
7 that management of the acute condition should take precedent. New ADHD medication
8 should not be started in this context and any existing ADHD medication should be stopped
9 until the acute psychotic or manic episode has resolved.

10 **1.6.2 Cost effectiveness and resource use**

11 One economic evaluation was included from the previous guideline (King 2006). This was a
12 Health Technology Assessment including an original economic model looking at different 3
13 treatment strategies, with clinical effect based on a Network Meta-Analysis, for a child
14 population. This is partially applicable because of the population as it includes some studies
15 in the network meta-analysis that were only in a responder group. Limitations include no
16 dependence assumed between different drugs in the sequence, and only a small sample of
17 clinical evidence was used. The results of this are discussed below when talking about
18 dexamphetamine specifically 5 studies that were previously included in the last guideline
19 were selectively excluded because of reasons including; prior to the date cut-off, outcomes
20 used, and perspective.

21 Three new economic evaluations were identified for this question (two in children and one in
22 adults), but only some of the subgroups included in the children studies fulfil the population
23 criteria for this question.

24 Cottrell 2008 used a decision model to compare an algorithm with atomoxetine as first line
25 treatment versus an algorithm of standard treatment (the same sequence without
26 atomoxetine) in different child subgroup populations (included for this question are those who
27 are stimulant naïve, or stimulant contraindicated (naïve)). The other subgroups of patients
28 who have tried and failed stimulants or could not tolerate them are included in the
29 sequencing question. The study found that the interventions in each subgroup of the
30 atomoxetine algorithms were cost effective compared to the comparator algorithms. This
31 study was rated as partially applicable because although it was a UK study, it does not use
32 EQ-5D and valuations of the states are based on parents not the general public. It has
33 potentially serious limitations which include; a potential conflict of interest as it is funded by
34 the makers of atomoxetine, methods were sometimes unclear, the effectiveness data is
35 based on some clinical data that has been excluded for this question, and no adverse event
36 costs or other resource use costs included.

37 The second child study (Hong 2009) adapted the model from the UK study to a Spanish
38 context, however it compared sequences of atomoxetine as first line versus atomoxetine as
39 second line (and did not include dexamphetamine in the sequence). Therefore the
40 interventions were different, and it only looked at some of the subgroups that the UK paper
41 looked at (again only some of which are included in this review; stimulant naïve patients, and
42 stimulant naïve patients with contraindications), therefore the models were felt sufficiently
43 different to be included as separate studies. Note that although these studies compare
44 sequences in different ways, they are both essentially looking at which drug you should start
45 with. This study found that the intervention sequences were not cost effective. This is most
46 likely due to the higher european prices of the drugs. This study was also rated as being
47 partially applicable with potentially serious limitations as it is an update of the Cottrell study
48 and therefore has some of the same limitations.

49 The single study identified in adults (Zimovetz 2017) used a decision model to compare
50 Lisdexamfetamine (LDX) with Atomoxetine (ATX) and extended release Methylphenidate

1 (ER-MPH). This study found that LDX dominated both ATX and ER-MPH. This study was
2 rated as directly applicable because it was from a UK NHS perspective and used EQ-5D
3 data for QALYs. It has potentially serious limitations such as a potential conflict of interest as
4 it is funded by the makers of a LDX product, also no additional treatment was assumed
5 following non response/discontinuation. It conducted a network meta-analysis for treatment
6 effect and discontinuations and some studies in their NMA were not included in the guideline
7 clinical review.

8 Costs of the interventions identified from the clinical review and the main drugs used were
9 presented. Modified release preparations of methylphenidate are more expensive than the
10 short acting version. Other drugs that are more expensive are guanfacine, atomoxetine,
11 dexamphetamine, and lisdexamfetamine. The stimulants and atomoxetine are the main
12 drugs used for ADHD. Guanfacine is relatively new and only licensed for children who are
13 not suitable for stimulants.

14 It had become apparent during discussions that one drug in particular had drastically
15 increased in price since the previous guideline – dexamphetamine. Costing the
16 dexamphetamine dose used in King 2006 showed that this has increased in price by over
17 800%. Two included economic evaluations that included this drug as part of the sequence
18 were King 2006 and Cottrell 2008. As this information is likely to impact the cost
19 effectiveness of the interventions, the health economist replicated the King 2006 model by
20 updating only the drug prices as an informal exercise to see what this impact might be. This
21 confirmed that the most cost effective strategy was now Methylphenidate IR – Atomoxetine –
22 Dexamfetamine – No treatment, rather than the base case result from the study of;
23 Dexamfetamine – Methylphenidate IR – Atomoxetine – No treatment. The increased price of
24 Dexamfetamine means it is no longer cost effective first or second line even though it has a
25 higher response rate and fewer withdrawals than the other drugs. The increased cost is
26 outweighing the additional benefit.

27 With regards to the Cottrell study that also includes dexamphetamine in its sequences, this
28 was more difficult to replicate from the paper as it was a markov model and the paper wasn't
29 clear enough about the model structure. We can however make assumptions about what the
30 impact of a price change of this drug would be; The intervention arm for each subgroup
31 always had atomoxetine first followed by other treatments, and the comparator sequence
32 was the same sequence but without atomoxetine. Because of this, dexamfetamine will
33 always be closer to the front of the sequence in the comparator arm. Meaning that in the
34 comparator arm, more people will be on dexamfetamine because you only go on to the next
35 treatment if you fail the previous one. Therefore a dexamfetamine price increase will increase
36 the total cost of the comparator arm more than the total cost of the intervention arm,
37 therefore making the incremental cost smaller and the intervention arm more cost effective. It
38 may even make the intervention cost saving.

39 As well as the interventions themselves, other resource should be considered such as
40 appointments with staff including GPs, psychiatrists, and paediatricians. Some interventions
41 already used in current practice such as atomoxetine are slow to act compared to stimulants,
42 and it can take weeks for any improvement to be seen. This implies that atomoxetine may
43 have more infrequent monitoring in the initial phase compared to stimulants because of the
44 duration of action. Adverse events also need to be monitored which affect resource use.

45 If UK evidence is prioritised higher weight would be given to King 2006, Cottrell 2008, and
46 Zimovetz 2017. The first two studies tell us that different sequences are cost effective that
47 still involve the 3 main drugs - atomoxetine, dexamfetamine (or lisdexamfetamine, that has
48 the same active component), and methylphenidate, and the study in adults informs that
49 lisdexamfetamine could be more cost effective than atomoxetine and extended release
50 methylphenidate. Overall a mixed picture, but these are the 3 that have been recommended
51 previously and remain at the top of the treatment algorithms in this update. Sequences of
52 treatment are discussed in more detail below.

11.6.2.1.1 **Cost effectiveness and resource use for children under the age of 5**

2 See the non-pharmacological review and rationale for more information about these
3 recommendations.

4 For pre-school children, drug treatment was previously not recommended. The GC
5 discussed that there are some cases where a pre-school child's ADHD could be particularly
6 severe that drug treatment might be initiated. The GC therefore felt that they would add a
7 caveat to make clear that only after parent training has been unsuccessful (if still causing
8 severe impairment) should a tertiary care specialist be contacted for further opinion on the
9 initiation of drugs.

10 It was also discussed how the age range for pre-school children should be defined more
11 specifically, and this was agreed to be under the age of 5. Aged 5 and over would be school
12 aged children. This may have resource implications if traditionally school age was defined as
13 6 and above in the previous guideline. The clinical studies included for pre-school children go
14 up to the age of, and including, 6 years old. If the threshold for treatment with medication is
15 being lowered then this could mean there may now be additional children that could be using
16 interventions for ADHD, which would have a resource impact. It is however largely practice
17 that as school age in England is 5 years old that most practice is to use medication in
18 children aged 5 and above if felt appropriate.

191.6.2.1.2 **Cost effectiveness and resource use for children aged 5 to 18**

20 Taking all of this information alongside the economic evidence;

21 The study on adults showed that LDX was cost effective compared to atomoxetine or
22 extended release methylphenidate. Assuming this could be extrapolated to a child
23 population, and taken together with the clinical evidence on the effectiveness of stimulants
24 led the committee to consider that lisdexamfetamine should also be a first line option
25 alongside methylphenidate preparations but recognised that the licensing status of the drugs
26 prevented this. If stimulants cannot be tolerated or trials of methylphenidate and LDX have
27 not worked (including trying higher doses) then the next line of drug treatment was decided
28 as atomoxetine or guanfacine (in children only). UK economic evaluations showed that;
29 atomoxetine was cost effective first line (Cottrell study), and also second line (following IR-
30 MPH – King study), and as mentioned above not cost effective compared to
31 lisdexamfetamine.

32 All of this is a mixed picture, but again taking it together with the clinical evidence that
33 atomoxetine is no better than methylphenidate, is more expensive and takes longer to work
34 led the committee to recommend atomoxetine after stimulants in the ordering of treatments.
35 Guanfacine was not available at the time of the previous guideline. Clinical evidence was
36 identified to show that guanfacine and extended release guanfacine (only extended release
37 guanfacine is listed in the BNF at this time and licensed for children) had clinical benefit
38 compared to placebo. One large clinical study found that guanfacine had a clinical benefit
39 compared to atomoxetine but the committee noted the greater number of studies about
40 atomoxetine than guanfacine and they were of higher quality. Members of the committee
41 agreed there was currently more clinical experience with atomoxetine than guanfacine. No
42 economic evidence was found for guanfacine in this question. However the further down the
43 treatment pathway we go the smaller the population that will be using those treatments
44 because it is only those people who cannot tolerate or do not respond to the previous
45 treatments in the sequence. At this point if someone has failed the treatments thus far (at
46 least one stimulant and one non-stimulant), anything else should only be prescribed in the
47 context of tertiary services or at minimum a second opinion should be obtained from a
48 healthcare professional with specialist knowledge of ADHD.

49 For most subgroups of people with ADHD and a co-existing condition, the sequence is the
50 same, although there are exceptions where the committee wanted to alter the sequence

1 depending on the co-morbidity or risk factors such as risk of misuse. These were consensus
2 based recommendations.

3 The committee consensus was that drug treatment would currently be offered to school age
4 children as it is considered to be more effective than no treatment as demonstrated by the
5 clinical review. And also as demonstrated by some of the cost effectiveness evidence (e.g.
6 the sequence from Cottrell that compared atomoxetine followed by no treatment versus no
7 treatment which had an ICER of under £12,000). A discussion on pharmacological treatment
8 versus other treatments (e.g. non-pharmacological) can be found in the combination review.

9 Although it is already current practice, there may be a resource impact from this
10 recommendation because the previous guideline separated those with moderate impairment
11 from those with severe impairment, and drug treatment was only offered first line to those
12 with severe impairment. It was not possible in this update to divide the populations by
13 severity. The committee recommended offering medication to children and young people
14 over 5 years old if their ADHD symptoms are having a significant impact on at least one
15 domain of their everyday life even after environmental modifications. This may include some
16 people who were previously categorised as being of moderate severity from the classification
17 of the previous guideline. There is difficulty in practice in defining the severity of ADHD and
18 an element of clinician judgement is needed. The opinion of the committee was although this
19 may mean more people could receive drugs than the previous guideline, in practice the help-
20 seeking population are likely to be mostly made up of children who meet the criteria for more
21 severe ADHD rather than moderate, and so the impact may be small.

221.6.2.1.3 **Cost effectiveness and resource use for adults aged over 18**

23 The pathway begins the same as for children by recommending stimulants as first line. As
24 mentioned previously, one economic evaluation for adults was identified comparing
25 lisdexamfetamine to extended release methylphenidate and atomoxetine, and found that
26 lisdexamfetamine was dominant. The clinical review found that both formulations of
27 methylphenidate were effective compared to placebo. Lisdexamfetamine was also found to
28 have benefit compared to placebo. There weren't as many direct comparisons of different
29 drugs for adults however as there were for children. The licensing around some of the drugs
30 was also a factor in determining their placement in the pathway. Atomoxetine for example is
31 only licensed in adults if they had childhood symptoms. Therefore atomoxetine was a second
32 line treatment for adults, followed by a referral to tertiary services before guanfacine could be
33 prescribed in adults because it is not licensed for adults.

34 The wording of the recommendation was altered to ensure that those receiving drugs will be
35 those for whom their ADHD has a significant impact on at least one domain of their everyday
36 life after environmental modifications. The opinion of the committee was that not all adults
37 with ADHD (those considered moderate or severe from the last guideline) currently receive
38 drug treatment, and so there is unlikely to be a resource impact from this recommendation.

391.6.2.1.4 **Cost effectiveness and resource use summary**

40 The sequences of drugs involved had to be based on a number of different factors; the
41 clinical evidence, the economic evidence, cost considerations, side effect profiles,
42 consensus, and it was challenging to bring all the information together when faced with lots
43 of pairwise comparisons and models comparing different sequences and have to make
44 indirect comparisons between treatments. There is uncertainty as to which sequence of
45 drugs is the most cost effective because some of the economic evidence identified is
46 conflicting. It is also important to remember that there is a distinction between the continuous
47 outcomes that the clinical review is using for decision making, and the outcomes that tend to
48 be used in models which are dichotomous outcomes. Ideally a network meta-analysis using
49 the clinical evidence could have informed an economic model but there is data lacking on
50 specific sequences of treatment that would be needed for dependent probabilities of
51 response.

1 **1.6.3 Other factors the committee took into account**

2 The committee noted that in their experience there was a very high non acceptance of
3 pharmacological treatments in the under 5 years age group and this was true of the high
4 dropout rate in some of the studies. This they agreed supported their recommendation on not
5 recommending medication for the under 5s without a specialist referral.

6 **1.7 The committee's discussion of the evidence for**
7 **sequencing pharmacological treatment**

8 **1.7.1 Interpreting the evidence**

9 **1.7.1.1 The outcomes that matter most**

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

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

19 **1.7.1.2 The quality of the evidence**

20 Most outcomes were graded as low or very low quality. The downgrades tended to be for a
21 combination of risk of bias and imprecision. Risk of bias was assessed as high or very high
22 for a number of reasons though most commonly due to incomplete reporting of blinding
23 methodology utilised in the study. The other influential risk of bias domains were selection of
24 participants, and incomplete outcome data. Imprecision was serious for over ninety per cent
25 of the outcomes.

26 Some treatment comparisons had outcomes of higher quality; lisdexamfetamine , dimesylate
27 versus atomoxetine had some outcomes considered to be of moderate quality. Risperidone
28 versus placebo had some outcomes considered to be of moderate quality and one of high
29 quality.

30 There were 24 specific treatments and additionally six separate classes (for example SSRIs)
31 of treatments detailed in the protocol. There were zero randomised controlled trials (RCTs) in
32 the pre-school children strata, six RCTs included in the children and young people strata and
33 one RCT in the adults strata. There were many treatments or combinations of treatments
34 combined with additionally previously received medication for ADHD to which participants
35 were intolerant or non-responsive not covered in these included trials.

36 The committee noted that there was only a single very small trial assessing the impact of
37 combined methylphenidate and atomoxetine, reporting very low quality outcomes. This was
38 highlighted as an area where further research would be important.

39 **1.7.1.3 Benefits and harms**

40 **1.7.1.3.1 Children under the age of 5**

41 In addition to the scarcity of evidence on anything other than methylphenidate no sequencing
42 evidence was found in this age stratum. The committee did not make specific

1 recommendations on the sequence of medication to use in this group as they considered it to
2 be uncommon that medication was used in this age group and recommended it should only
3 be done after seeking expert advice.

41.7.1.3.2 **Children and young people aged 5 to 18**

5 *Methylphenidate versus placebo augmented on top of previous atomoxetine treatment.* No
6 clinical difference was found in terms of discontinuation of treatment due to adverse events
7 or adverse events leading to hospitalisation/death/disability.

8 *Guanfacine in the morning or evening versus placebo augmented on top of previous*
9 *stimulant treatment.* Both morning and evening administration of guanfacine showed no
10 clinical difference in terms of ADHD symptoms and early discontinuation of treatment due to
11 adverse events. There was a clinical benefit for guanfacine morning/evening in terms of the
12 CGI-I score and a clinical harm for guanfacine morning/evening in terms of adverse events
13 leading to hospitalisation/death/disability.

14 *Lisdexamfetamine dimesylate versus atomoxetine where previous methylphenidate*
15 *treatment was stopped.* There was a clinical benefit for ADHD symptoms (investigator rated),
16 ADHD symptoms hyperactivity/impulsivity subscale (investigator rated), ADHD symptoms
17 inattentiveness subscale (investigator rated), Weiss Functional Impairment Rating Scale -
18 Parent Report, and CGI-S improvement. There was no clinical difference in terms of
19 discontinued treatment due to adverse event or adverse events leading to
20 hospitalisation/death/disability.

21 *Risperidone versus placebo where previous methylphenidate treatment was continued.*
22 There was a clinical benefit for risperidone in terms of ADHD severity (parent rating) and the
23 corresponding inattention, hyperactivity and impulsivity subscales. This was fairly well
24 matched in the ADHD severity (teacher rating) where there was a clinical benefit for
25 risperidone in terms of overall severity and for impulsivity and inattention subscales. However
26 there was a clinical harm for risperidone for the hyperactivity subscale (teacher rating). There
27 was a clinical benefit for risperidone in the oppositional defiant disorder (ODD) DSM-IV
28 (parent rating), Peer Conflict Scale (parent rating), conduct disorder (CD) DSM-IV (parent
29 rating). There was no clinical difference in terms of ODD DSM-IV (teacher rating), Peer
30 Conflict Scale (teacher rating), CD DSM-IV (teacher rating).

31 *Lisdexamfetamine dimesylate versus placebo where previous methylphenidate treatment*
32 *was stopped.* A clinical benefit was found for lisdexamfetamine dimesylate for clinical
33 response and no clinical difference for adverse events leading to
34 hospitalisation/death/disability.

35 *Clonidine versus placebo where previous stimulant treatment continued.* There was a clinical
36 benefit for clonidine for ADHD symptoms (investigator rated) and both inattention and
37 hyperactivity/impulsivity subscales. There was no clinical difference for CGI-I and
38 discontinued treatment due to TEAE.

391.7.1.3.3 **Adults over 18**

40 *Guanfacine versus placebo where previous CNS stimulant treatment continued.* No clinical
41 difference was found for ADHD symptoms or adverse events leading to
42 hospitalisation/death/disabilities.

431.7.1.3.4 **Summary**

44 The committee considered that the body of evidence in general did not support the use of
45 combined therapies other than in the very specific situations outlined in the
46 recommendations for risperidone. The majority of the sequencing trials included in this
47 review were smaller and varied greatly; this mean they couldn't be combined to increase the
48 power. As a whole the evidence was of lower quality than the trials assessing the

1 effectiveness of medication, they also predominantly compared adding/substituting with a
2 new medication and not adding/substituting with placebo. Therefore the committee broadly
3 based their recommendations around the sequence of medication on the body of efficacy
4 evidence in the general pharmacological efficacy review.

5 **1.7.2 Cost effectiveness and resource use**

6 Seven economic evaluations (cost utility analyses) were identified for this review question. All
7 were in children. Two of these have already been included in the effectiveness of
8 pharmacological treatments review, however particular subgroups are included here because
9 they were considered to be subgroups that had previously been exposed to stimulant
10 medication and either failed or could not tolerate it. The populations included here from
11 Cottrell 2008 are; stimulant failed patients, stimulant averse (exposed) patients, and
12 stimulant contraindicated (exposed) patients. This compared algorithms with atomoxetine
13 first line with algorithms that did not include atomoxetine, in a 1 year markov model, and
14 found that the intervention arms (that included atomoxetine as first line) were cost effective
15 for all subgroups. The study was rated as partially applicable because it was a UK study with
16 an NHS cost perspective. However it does not use EQ-5D and valuations of the states are
17 based on parents not the general public. It has potentially serious limitations with reasons
18 including; it has a potential conflict of interest, methods were sometimes unclear, effect was
19 based on some data that has been excluded for this question and no adverse event costs or
20 other resource use costs were included.

21 Hong 2009 was also included in the pharmacological effectiveness review, and one
22 subgroup of stimulant failed patients is included in this review. This is a Spanish adaptation
23 of the Cottrell study, and the intervention compares atomoxetine with no treatment.
24 Atomoxetine was not found to be cost effective here, and this is most likely because of the
25 higher price of the drug compared to the Cottrell study. This study is also partially applicable
26 and with potentially serious limitations, for similar reasons to Cottrell because they are based
27 on the same data.

28 Three studies compare types of extended release methylphenidate with immediate release
29 methylphenidate in children who are responding sub-optimally to immediate release
30 methylphenidate because of inadequate medication intake. Faber 2008 was a Markov model
31 with a 10 year time horizon. The markov model is preceded by a 2 month primary phase.
32 Patients going into the primary phase are youths with sub optimal symptom control from
33 methylphenidate immediate release, but from this group only those who are responding to
34 immediate release methylphenidate but the treatment is suboptimal due to inefficient
35 exposure because of the multiple daily administration are required go into the markov phase.
36 Staying on IR MPH is then compared to optimal response with OROS MPH (a type of
37 extended release MPH). There are 4 states in each arm (not the same for both arms). The
38 study found OROS MPH to be cost effective. This was rated as partially applicable because
39 it is a non UK study, it uses different but similar discount rates to NICE, and does not use
40 EQ-5D and utilities are not from the public. It has potentially serious limitations such as a
41 potential conflict of interest, a lot of assumptions/inputs from a panel of experts and limited
42 data. Van der Schans 2015 is an updated version of the Faber model using slightly different
43 health states and inputs. It also compares different versions of modified release
44 methylphenidate (OROS MPH, or Medikinet CR/Equasym XL (these two interventions were
45 grouped together)). This study found that MPH OROS was cost effective versus immediate
46 release MPH, but that Medikinet/Equasym was dominant versus immediate release MPH.
47 The Medikinet/ Equasym comparator is dominant overall because it is cheaper than MPH
48 OROS and has the same QALYs. The applicability and quality rating given to the study was
49 the same as for Faber 2008. The final of these three studies was Schawo 2015. This was
50 again based on Faber but some structural aspects of the model were slightly different such
51 as a 12 year time horizon and different assumptions about health states. Schawo found that
52 OROS MPH was dominant. This study was also partially applicable with very serious
53 limitations because it makes the most assumptions of the three. The three studies comparing

1 extended release methylphenidate to immediate release have a range of results, although
2 they are all pointing in the same direction, and this is most likely because of a number of
3 structural and data differences in the three models.

4 Lachaine 2016 is a Canadian study that used a 1 year markov model to compare adding
5 guanfacine extended release onto a long-acting stimulant versus long-acting stimulants
6 alone in children who are only partially responding to the stimulant. This study showed that
7 the addition of guanfacine was cost effective, and was assessed as partially applicable
8 because of the healthcare system with potentially serious limitations as it is only based on a
9 single short term trial and has a conflict of interest as the funders make guanfacine.

10 The final study was a UK study that used a 1 year decision tree to compare
11 lisdexamfetamine with atomoxetine in children who had an inadequate response to
12 methylphenidate. The study found that lisdexamfetamine was cost effective compared to
13 atomoxetine, and was rated as directly applicable because it is UK, and had potentially
14 serious limitations because similarly to the other studies it is funded by the makers of the
15 intervention and is based on a single short term trial.

16 No evidence was found in adults.

17 In summary of the evidence, there is conflicting evidence about atomoxetine, as UK evidence
18 found an algorithm including atomoxetine first line is cost effective, but not when a single line
19 of treatment of atomoxetine is compared to lisdexamfetamine. Extended release
20 methylphenidate versus immediate release in patients with suboptimal response to
21 immediate release methylphenidate was found to be cost effective or dominant. However as
22 they are the same drug, then extended release methylphenidate is essentially only solving
23 the issue of compliance, and if patients were compliant to immediate release
24 methylphenidate then they would be just as effective and immediate release methylphenidate
25 is less costly. A study on guanfacine, although not from the UK, found that it is a cost
26 effective addition. It is important to bear in mind though that augmenting existing treatment
27 with another drug means that the costs of two drugs will apply, and the committee felt that
28 there was not enough clinical and economic evidence to say that two treatments together
29 might be better than one.

30 In summary the it is difficult to draw conclusions; although there is some UK evidence
31 showing that atomoxetine first line is cost effective (in people who have tried stimulants),
32 there is also have evidence saying that lisdexamfetmine is cost effective compared to
33 atomoxetine in children who are partially responding to methylphenidate (and clinical
34 evidence supports this also). Hence in people who may have tried stimulants before and
35 either cannot tolerate or have failed them, the committee agreed that lisdexamfetamine and
36 atomoxetine are likely to be choices that might be tried next in the pathway. There is no
37 economic evidence directly comparing guanfacine with other treatments, only the Lachaine
38 study which looked at guanfacine as an adjunct to stimulant treatment (versus stimulant
39 treatment alone). More discussion around how the order of the drug treatments in the
40 pathway was decided can be found in the pharmacological effectiveness rationale section
41 above.

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1 **Appendices**
2 **Appendix A: Review protocols**
3 **A.1 Pharmacological efficacy**

4 **Table 72: Review protocol: Pharmacological efficacy**

Field	Content
Review question	What is the most clinically and cost-effective pharmacological treatment for children, young people and adults 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	Inform recommendations into which drugs to use for people with ADHD when medication is indicated
Eligibility criteria – population / disease / condition / issue / domain	Children, young people and adults with ADHD Stratified by: Age – under 5, 5 to 18, over 18
Eligibility criteria – interventions	The following treatments (all doses), received for a minimum of 2 weeks: Methylphenidate Methylphenidate modified release Dexamphetamine Lisdexamfetamine dimesylate Atomoxetine Guanfacine Clonidine Tricyclic antidepressants SSRIs SNRIs MAOIs Risperidone Olanzapine Clozapine Haloperidol Quetiapine Aripiprazole Carbamazepine Valproate Lamotrigine Lithium Asenapine Buspirone Bupropion Nicotine Modafinil Melatonin

Field	Content
	Sativex Acetylcholinesterase inhibitors Antiparkinson medication Combinations of the above
Eligibility criteria – comparator(s) / control or reference (gold) standard	Placebo Each other
Outcomes and prioritisation	<p>Critical</p> <p>Quality of life [continuous] ADHD symptoms (total; parent) [continuous] [children and young people] ADHD symptoms (total; teacher) [continuous] [children and young people] ADHD symptoms (total; self-rated in young people 13-18 years and adults) [continuous] ADHD symptoms (total; carer/partner) [continuous] [adults] ADHD symptoms (total; investigator) [continuous] ADHD symptoms (inattention; parent) [continuous] [children and young people] ADHD symptoms (inattention; teacher) [continuous] [children and young people] ADHD symptoms (inattention; self-rated in young people 13-18 years and adults) [continuous] ADHD symptoms (inattention; carer/partner) [continuous] [adults] ADHD symptoms (inattention; investigator) [continuous] ADHD symptoms (hyperactivity; parent) [continuous] [children and young people] ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people] ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous] ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults] ADHD symptoms (hyperactivity; investigator) [continuous] Clinical Global Impressions scale (improved or much improved) [dichotomous]</p> <p>Important</p> <p>Serious adverse events (all) [dichotomous] Behavioural (children)/Functional (adults) measures [continuous] Emotional dysregulation [continuous] Academic outcomes (children) [continuous] Substance use (alcohol and drug use) [dichotomous] Self-harm [dichotomous]</p> <p>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.</p> <p>ADHD symptoms outcomes to be preferentially extracted as continuous outcomes where available. If only dichotomous outcomes available</p>

Field	Content
	from individual study, dichotomous outcomes will be extracted.
Eligibility criteria – study design	Blinded RCTs only
Other inclusion exclusion criteria	<p>Studies will be excluded if ADHD diagnosis made not using DSM-III or ICD-10 or later versions. Studies evaluating treatments for ADHD in a population of people with autistic spectrum disorder will be included if no formal diagnosis of ADHD is made but there is evidence of moderate to severe symptoms of hyperactivity, impulsivity and/or inattention through validated symptom questionnaires.</p> <p>Crossover trials will be excluded if there is an inappropriate washout period (specific to pharmacokinetics of drug involved)</p> <p>Studies will be excluded if the population is selected entirely on the basis of being responders to the drug under investigation (e.g. inclusion criteria previously responded to methylphenidate, interventions are methylphenidate and placebo)</p>
Proposed sensitivity / subgroup analysis, or meta-regression	<p>Presence or absence of co-existing conditions (inc. intellectual disability, ASD, epilepsy, affective disorders, tic disorder, personality disorder, addiction, CD/ODD)</p> <p>Additional age groups (13-18, 18-25, 25-65, >65)</p> <p>Severity (mild, moderate severe)</p> <p>Dose (low, medium, high)</p> <p>Diagnostic method (DSM vs ICD)</p> <p>Region (UK vs Europe vs US vs Japan)</p> <p>Setting (looked after/secure estate vs general)</p> <p>Titration (fixed dose vs titrated)</p>
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)	<p>Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).</p> <p>GRADEpro was used to assess the quality of evidence for each outcome.</p> <p>Endnote for bibliography, citations, sifting and reference management.</p>
Information sources – databases and dates	<p>Clinical search databases to be used: Medline, Embase, Cochrane Library, PsycINFO</p> <p>Date: From October 2007</p> <p>Health economics search databases to be used: Medline, Embase, NHSEED, HTA</p> <p>Date: Medline, Embase from 2014</p> <p>NHSEED, HTA – from 2008</p> <p>Language: Restrict to English only</p> <p>Supplementary search techniques: backward citation searching</p> <p>Key papers: Not known</p>
Identify if an update	Yes, 2009
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	For details please see evidence tables in Appendix D (clinical evidence

Field	Content
variables to be collected	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 section 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 section 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

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Table 73: 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

Review question	All questions – health economic evidence
	<p>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.</p>
Search strategy	<p>A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B [in the Full guideline]. 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</p>
Review strategy	<p>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.</p> <p>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.</p> <p>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).⁴⁷³</p> <p>Inclusion and exclusion criteria</p> <p>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.</p> <p>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.</p> <p>If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</p> <p>Where there is discretion</p> <p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <ul style="list-style-type: none"> 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). <p>Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.</p> <p>Health economic study type:</p> <ul style="list-style-type: none"> Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).

Review question	All questions – health economic evidence
	<p>Comparative cost analysis.</p> <p>Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.</p> <p>Year of analysis:</p> <p>The more recent the study, the more applicable it will be.</p> <p>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'.</p> <p>Studies published before 2001 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.</p> <p>Quality and relevance of effectiveness data used in the health economic analysis:</p> <p>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.</p> <p>Economic evaluations that are based on studies excluded from the clinical review will be excluded.</p>

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2 A.2 Pharmacological sequencing

3 **Table 74: Review protocol: Sequence of pharmacological treatment**

Field	Content
Review question	What is the most clinically and cost-effective sequence of pharmacological treatment for children and young people and adults 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 sequence of pharmacological treatment for people with ADHD
Eligibility criteria – population / disease / condition / issue / domain	Children and adults with ADHD who have previously received medication for ADHD to which they are either intolerant or non-responsive Stratified by: <ul style="list-style-type: none"> • Age (children under 5, children and young people aged 5 to 18, adults aged 18 years and over) • Drug previously received • Drug response
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Antidepressants; Tricyclics Tricyclic antidepressants ; SSRIs Tricyclic antidepressants ; MNRIs Tricyclic antidepressants ; MAOIs Antipsychotics; Risperidone Antipsychotics; Quetiapine Antipsychotics; Olanzapine Antipsychotics; Clozapine Antipsychotics; Aripiprazole

	<p>Antipsychotics; Haloperidol CNS stimulants; Methylphenidate (including modified-release preparations) CNS stimulants; Atomoxetine CNS stimulants; Dexamphetamine CNS stimulants; Modafanil CNS stimulants; Lisdexamfetamine dimesylate Bupropion Nicotine; Nicotine skin patches Nicotine; Nicotine (other formulation) Clonidine No treatment No treatment; Standard treatment No treatment; Placebo Guanfacine Melatonin Mood stabilisers; Carbamazepine Mood stabilisers; Valproate Mood stabilisers; Lamotrigine Mood stabilisers; Buspirone Mood stabilisers; Lithium Mood stabilisers; Asenapine Sativex Anti-cholinesterase inhibitors Drugs used to treat Parkinson's disease (adults only) Combination of the above (including where a medication is added to the previous medication)</p>
Eligibility criteria – comparator(s) / control or reference (gold) standard	All interventions will be compared with each other, unless otherwise stated
Outcomes and prioritisation	<p>All outcomes to be measured at a short term (up to 3-months) and long-term (beyond 3 months) timepoints. Where multiple timepoints are reported within each definition, the longest timepoint only will be extracted.</p> <p>Critical</p> <ul style="list-style-type: none"> • Quality of life [continuous] • ADHD symptoms (total; parent) [continuous] [children and young people] • ADHD symptoms (total; teacher) [continuous] [children and young people] • ADHD symptoms (total; self-rated in children 13-18 years and adults) [continuous] • ADHD symptoms (total; carer/partner) [continuous] [adults] • ADHD symptoms (total; investigator) [continuous] • ADHD symptoms (inattention; parent) [continuous] [children and young people] • ADHD symptoms (inattention; teacher) [continuous] [children and young people] • ADHD symptoms (inattention; self-rated in children 13-18 years and adults) [continuous] • ADHD symptoms (inattention; carer/partner) [continuous] [adults]

	<ul style="list-style-type: none"> • ADHD symptoms (inattention; investigator) [continuous] • ADHD symptoms (hyperactivity; parent) [continuous] [children and young people] • ADHD symptoms (hyperactivity; teacher) [continuous] [children and young people] • ADHD symptoms (hyperactivity; self-rated in children 13-18 years and adults) [continuous] • ADHD symptoms (hyperactivity; carer/partner) [continuous] [adults] • ADHD symptoms (hyperactivity; investigator) [continuous] • Clinical Global Impressions scale (improved or much improved) [dichotomous] <p>Important</p> <ul style="list-style-type: none"> • Serious adverse events (all) [dichotomous] • Behavioural (children)/Functional (adults) measures [continuous] • Emotional dysregulation [continuous] • Academic outcomes (children) [continuous] • Substance use (alcohol and drug use) [dichotomous] • Self-harm [dichotomous]
Eligibility criteria – study design	<p>Systematic review RCT Unit of randomisation: patient, site</p>
Other inclusion exclusion criteria	<p>Crossover studies permitted Minimum length of treatment 2-weeks</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Open label trials • Crossover trials with inappropriate washout period • Treatment duration <2 weeks • ADHD diagnosis made not using DSM-III or ICD-10 or later versions. Studies evaluating treatments for ADHD in a population of people with autistic spectrum disorder will be included if no formal diagnosis of ADHD is made but there is evidence of moderate to severe symptoms of hyperactivity, impulsivity and/or inattention through validated symptom questionnaires.
Proposed sensitivity / subgroup analysis, or meta-regression	<ul style="list-style-type: none"> • Presence or absence of co-existing conditions (inc. intellectual disability, ASD, epilepsy, affective disorders, tic disorder, personality disorder, addiction, CD/ODD) • Additional age groups (13-18, 18-25, 25-65, >65) • Severity (mild, moderate severe) • Dose (low, medium, high) • Diagnostic method (DSM vs ICD) • Region (UK vs Europe vs US vs Japan) • Setting (looked after/secure estate vs general) Titration (fixed dose vs titrated)
Selection process – duplicate screening / selection / analysis	<p>No duplicate screening was deemed necessary for this question, for more information please see the separate Methods report for this guideline.</p>
Data management (software)	<ul style="list-style-type: none"> • Pairwise meta-analyses were performed using Cochrane Review

	<p>Manager (RevMan5).</p> <ul style="list-style-type: none"> • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote for bibliography, citations, sifting and reference management.
Information sources – databases and dates	<p>Clinical search databases to be used: Medline, Embase, Cochrane Library, PsycINFO</p> <p>Date: From October 2007</p> <p>Health economics search databases to be used: Medline, Embase, NHSEED, HTA</p> <p>Date: Medline, Embase from 2014</p> <p>NHSEED, HTA – from 2008</p> <p>Language: Restrict to English only</p> <p>Supplementary search techniques: backward citation searching</p> <p>Key papers: Not known</p>
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/cg72
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
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	<p>Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual</p> <p>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/</p>
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.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	<p>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.</p> <p>Staff from NGC undertook systematic literature searches, appraised the</p>

	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

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Table 75: 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	<p>Populations, interventions and comparators must be as specified in the clinical review protocols in appendix A above.</p> <p>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).</p> <p>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.)</p> <p>Unpublished reports will not be considered unless submitted as part of a call for evidence.</p> <p>Studies must be in English.</p>
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	<p>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.</p> <p>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.</p> <p>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).⁴⁷³</p> <p>Inclusion and exclusion criteria</p> <p>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.</p> <p>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.</p> <p>If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.</p>

Review question	All questions – health economic evidence
	<p>Where there is discretion</p> <p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p>Setting:</p> <p>UK NHS (most applicable).</p> <p>OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).</p> <p>OECD countries with predominantly private health insurance systems (for example, Switzerland).</p> <p>Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.</p> <p>Health economic study type:</p> <p>Cost–utility analysis (most applicable).</p> <p>Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).</p> <p>Comparative cost analysis.</p> <p>Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.</p> <p>Year of analysis:</p> <p>The more recent the study, the more applicable it will be.</p> <p>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’.</p> <p>Studies published before 2001 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.</p> <p>Quality and relevance of effectiveness data used in the health economic analysis:</p> <p>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.</p> <p>Economic evaluations that are based on studies excluded from the clinical review will be excluded.</p>

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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>. The same literature search strategies were used for the 2 review questions in this review, pharmacological efficacy and pharmacological sequencing.

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 76: 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)

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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)

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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
#19.	#9 and #17

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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)

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4 B.2 Health Economics literature search strategy

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

10 **Table 77: 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
Centre for Research and	HTA - 2008 – 28 April 2017	None

Database	Dates searched	Search filter used
Dissemination (CRD)	NHSEED - 2008 to March 2015	

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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)

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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)

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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

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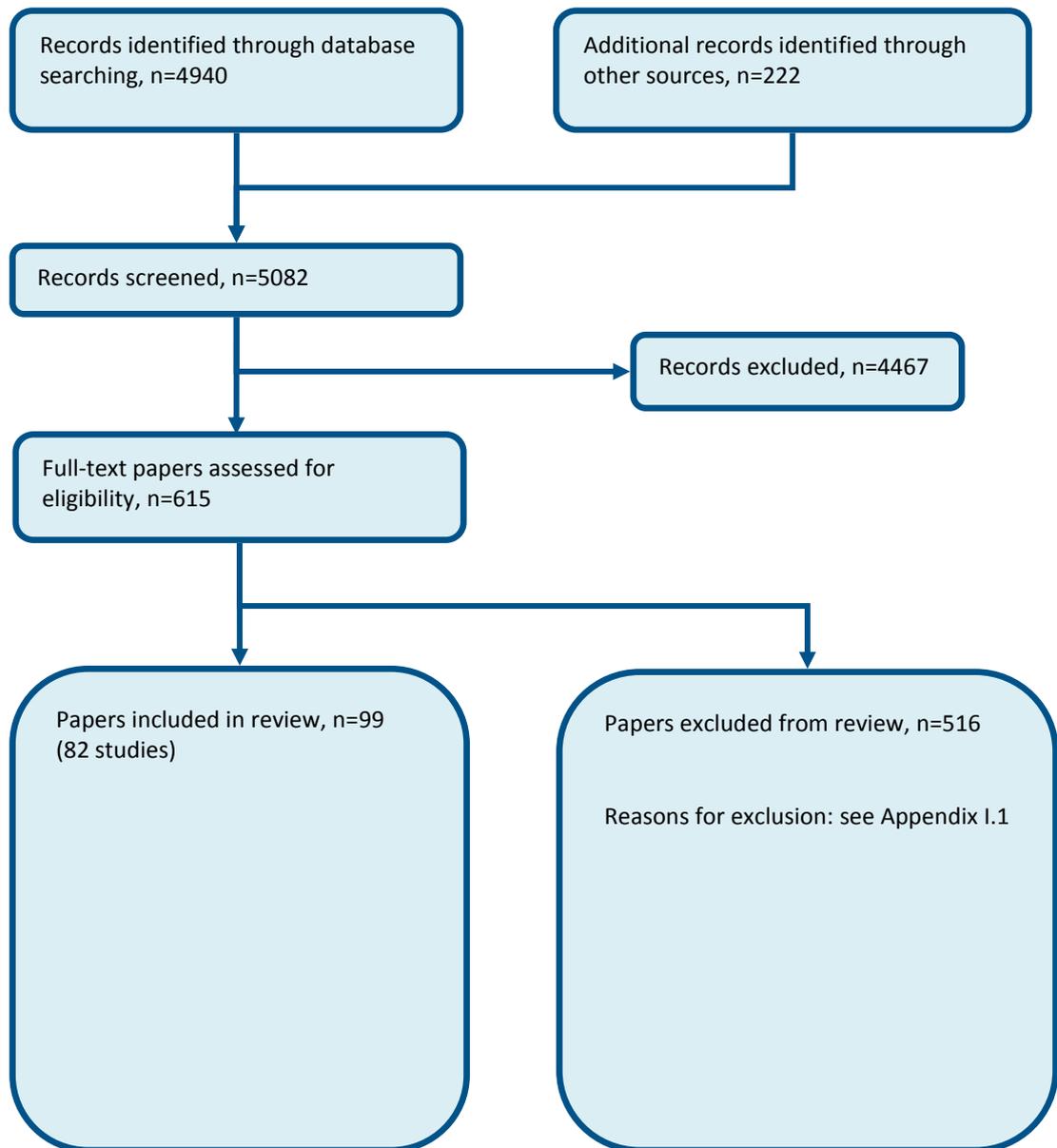
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Appendix C: Clinical evidence selection

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C.1 Pharmacological efficacy

Figure 1: Flow chart of clinical study selection for the review of the most clinically and cost-effective first-line pharmacological treatment for people with ADHD?



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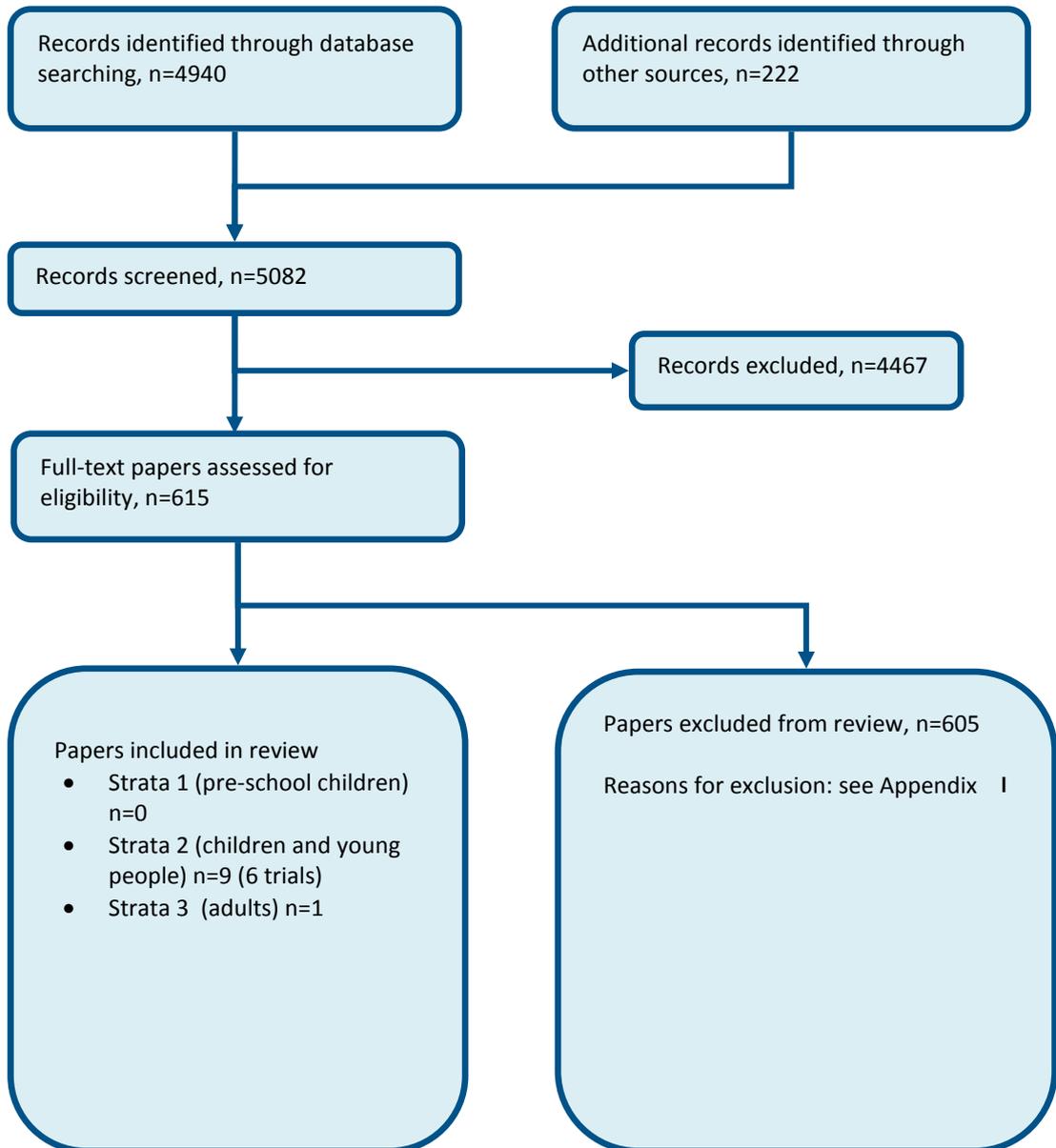
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2 C.2 Pharmacological sequencing

Figure 2: Flow chart of clinical study selection for the review of pharmacological treatment sequencing



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Appendix D: Clinical evidence tables

D.1 Pharmacological efficacy

Study	Abikoff 2009 ³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=19)
Countries and setting	Conducted in USA; Setting: New York
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD-RS ADHD symptoms of at least 1.5SDs above the norm for age and sex. Impaired organization, time management and planning defined by a mean score of at least 1SD below the norm on the COSS-T or COSS-P, and at least a score on 80 on WASI.
Exclusion criteria	Autism, major depression, substance abuse, OCD, PTSD, panic disorder, tic disorders, significant suicidality or a lifetime history of psychosis or mania. Learning disabilities also excluded.
Recruitment/selection of patients	Via mailings to schools, clinics, community practitioners and newspaper adverts.
Age, gender and ethnicity	Age - Range: 8 to 13 years. Gender (M:F): 15:4. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (26.3% ODD). 5. Diagnostic method: DSM 6. Line of treatment: 1st line (drug naive) 7. Severity: Mixed
Extra comments	All stimulant naive
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). The first 2 weeks involved flexible dosing schedules with the goal of titration to a maximum of 54mg/day. In some cases this period was extended by a week due to scheduling problems as a result of holidays or absences.

Study	Abikoff 2009 ³
	<p>The optima dose was maintained for the final 2 weeks. The mean length was 4.6 weeks (0.8SD) on methylphenidate and 4.5(0.8SD) on placebo. A 2 day washout ensued before crossing over the remaining intervention. Mean dose was 48.3mg on MPH-OROS and 52.1mg on placebo. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Moderate 2. Method of titration: Titrated to optimum dose</p> <p>(n=19) Intervention 2: No treatment - Placebo. The first 2 weeks involved flexible dosing schedules with the goal of titration to a maximum of 54mg/day. In some cases this period was extended by a week due to scheduling problems as a result of holidays or absences. The optima dose was maintained for the final 2 weeks. The mean length was 4.6 weeks (0.8SD) on methylphenidate and 4.5(0.8SD) on placebo. A 2 day washout ensued before crossing over the remaining intervention. Mean dose was 48.3mg on MPH-OROS and 52.1mg on placebo. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Moderate 2. Method of titration: Titrated to optimum dose</p>
Funding	Principal author funded by industry (Shire Pharmaceuticals and Novartis Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): SNAP-IV total scores teacher rated at 4 weeks; Group 1: mean 1.13 (SD 0.46); n=19, Group 2: mean 1.5 (SD 0.55); n=19

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): SNAP-IV hyperactivity subscores teacher rated at 4 weeks; Group 1: mean 0.72 (SD 0.51); n=19, Group 2: mean 1.16 (SD 0.65); n=19

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): SNAP-IV inattention subscores teacher rated at 4 weeks; Group 1: mean 1.55 (SD 0.6); n=19, Group 2: mean 1.84 (SD 0.64); n=19

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): SNAP-IV inattention subscores parent rated at 4 weeks; Group 1: mean 1.34 (SD 0.73); n=19, Group 2: mean 1.84 (SD 0.6); n=19

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Study	Abikoff 2009 ³
	<p>- Actual outcome for Children (up to 18 years): SNAP-IV hyperactivity subscores parent rated at 4 weeks; Group 1: mean 0.65 (SD 0.5); n=19, Group 2: mean 0.96 (SD 0.79); n=19</p> <p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome for Children (up to 18 years): SNAP-IV total scores parents rated at 4 weeks; Group 1: mean 0.99 (SD 0.55); n=19, Group 2: mean 1.4 (SD 0.63); n=19</p> <p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Adler 2013 ⁹ (Adler 2013 ⁸)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=161)
Countries and setting	Conducted in USA; Setting: 35 US clinical research sites
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Met full DSM-IV criteria for ADHD. Required to have (1) a close domicile relationship (e.g. with spouse or significant other) for 6 months or more prior to screening (to ensure the availability of an informant) (2) baseline BRIEF-A Global Executive Composite GEC T-score of 65+ (3) baseline total score of 28+ on the ADHD-RS-IV.
Exclusion criteria	(1) comorbid psychiatric conditions controlled for with prohibited medication or were uncontrolled with significant symptoms (2) cardiovascular disease (3) history of moderate to severe hypertension (4) ADHD that was well controlled on current ADHD therapy (5) a history of failure to respond to an adequate course of amphetamine therapy

Study (subsidiary papers)	Adler 2013 ⁹ (Adler 2013 ⁸)
Recruitment/selection of patients	From May 2010 to November 2010
Age, gender and ethnicity	Age - Range: 18 to 55 years. Gender (M:F): 83 male, 76 female. Ethnicity: 85.5% White, 10% Black or African American, 1.26% Asian, 1.26% American Indian or Alaska Native, 1.89% Other (Also included: 7.5% Hispanic or Latino)
Further population details	1. ADHD subtype: All/mixed subtypes (81.11% combined, 18.24% inattentive, 0.63% hyperactive-impulsive). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: 7. Severity:
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	<p>(n=80) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Taken at 7am. During the 4 week dose optimization period, treatment was initiated at 30mg/day and titrated in 20mg/week increments to optimal dose (up to 70mg per day). Titration was based on total score on the ADHD-RS-IV with adult prompts, CGI-I scores, adverse events, and clinical judgement. An optimal dose was considered to be reached if a participant demonstrated 30%+ reduction from baseline in total score on the ADHD-RS-IV and a CGI-I rating of 'improved' or 'very much improved'. A single dose reduction was also permitted during the dose optimization period. Patients were continued on their optimal dose during the 6 week dose maintenance period and no dose reductions were permitted during this. Duration 10 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:</p> <p>(n=81) Intervention 2: No treatment - Placebo. Identical capsules and dosage. Duration 10 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:</p>
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus PLACEBO

- Actual outcome: AAQoL mean change scores (all subscales reported separately) at 10 weeks;
 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, lack of efficacy, other reasons (3). 1 not stated

Protocol outcome 2: ADHD symptoms at <3- or >6-months

Study (subsidiary papers)	Adler 2013 ⁹ (Adler 2013 ⁸)
	<p>- Actual outcome: ADHD-RS-IV with adult prompts inattention subscale LS mean change scores (adjusted for baseline) at 10 weeks; Group 1: mean -21.4 (SD 12.34); n=79, Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, lack of efficacy, other reasons (3). 1 not stated</p> <p>- Actual outcome: ADHD-RS-IV with adult prompts hyperactivity/impulsivity subscale LS mean change scores (adjusted for baseline) at 10 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, lack of efficacy, other reasons (3). 1 not stated</p> <p>- Actual outcome: ADHD-RS-IV with adult prompts total scores LS mean change (adjusted for baseline) at 10 weeks; Group 1: mean -21.4 (SD 12); n=79, Group 2: mean -10.3 (SD 12.34); n=75; ADHD-RS-IV 0-54 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, lack of efficacy, other reasons (3). 1 not stated</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome: Drop out due to adverse events at 10 weeks; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Previous treatments not stated; Group 1 Number missing: 18, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, other reasons (3 participants). 1 not stated; Group 2 Number missing: 28, Reason: adverse events, protocol violation, withdrawn consent, lost to follow up, lack of efficacy, other reasons (3). 1 not stated</p>
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Adler 2008 ¹¹ (Mattingly 2013 ⁴³⁵ , Adler 2009 ¹⁰ , Kollins 2011 ³⁸⁰)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=420)
Countries and setting	Conducted in USA; Setting: New York. No further details

Study (subsidiary papers)	Adler 2008 ¹¹ (Mattingly 2013 ⁴³⁵ , Adler 2009 ¹⁰ , Kollins 2011 ³⁸⁰)
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Post-hoc subgroup analysis: Prior Amphetamine (AMPH) subgroup was defined as all participants who took AMPH products with a stop date on or after the screening date. An ADHD-RS-IV total score of >18 at screening in the prior AMPH subgroup was considered a suboptimal level of symptom control
Inclusion criteria	(1) ADHD diagnosis from DSM-IV (2) at least 6 of the DSM-IV-TR subtype criteria met (3) moderate to severe ADHD as rated by a clinician on ADHD-RS (scores 28 or above) (4) resting heart rate 40 to 100 bpm and other ECG criteria
Exclusion criteria	(1) Comorbid psychiatric diagnosis with significant symptoms (2) history of seizures (3) taking medications that affect the CNS or blood pressure (4) known cardiac abnormalities (5) pregnancy or lactation (6) positive urine drug results at screening or baseline (6) women of child bearing potential not on contraceptives or not abstinent
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 18 to 55 years. Gender (M:F): 228:192. Ethnicity: 83.1% white, 16.9% not specified.
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not specified). 2. Age: Adults 18-65 years (18-55 years). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear (Kollins 2011 contains data possibly relevant to a subgroup analysis of those with/without depression or substance use). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Extra comments	ADHD. The mean (SD) ADHD-RS-IV total score at screening for the prior amphetamine (AMPH) subgroup was 39.3 (7.0) for placebo and 41.50(5.7) for LDX. Duration of prior AMPH exposure was reported in the range of approximately 2 weeks to 13 years ; only one participant was treated for <4 weeks
Indirectness of population	No indirectness
Interventions	(n=119) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Following a 7 to 28 day washout period, patients were assigned to 30mg/day. No further details. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose). (n=117) Intervention 2: CNS stimulants - Lisdexamfetamine dimesylate. Following a 7 to 28 day washout

Study (subsidiary papers)	Adler 2008 ¹¹ (Mattingly 2013 ⁴³⁵ , Adler 2009 ¹⁰ , Kollins 2011 ³⁸⁰)
	<p>period, patients were assigned to 30mg/day for 1 week with a forced dose escalation to 50mg/day from weeks 2 to 4. No further details. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).</p> <p>(n=122) Intervention 3: CNS stimulants - Lisdexamfetamine dimesylate. Following a 7 to 28 day washout period, patients were assigned to 30mg/day for 1 week, 50mg/day for 1 week followed by 70mg/day for 2 weeks. No further details. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).</p> <p>(n=62) Intervention 4: No treatment - Placebo. Identical capsules. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).</p> <p>(n=352) Intervention 5: CNS stimulants - Lisdexamfetamine dimesylate. Overall efficacy population. LDX 30 mg + LDX 50 mg + LDX 70 mg groups combined. Duration 4 weeks. Concurrent medication/care: not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to fixed dose).</p> <p>(n=39) Intervention 6: CNS stimulants - Lisdexamfetamine dimesylate. LDX with prior AMPH treatment before screening. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=2) Intervention 7: No treatment - Placebo. Placebo group with prior MPH treatment before screening of trial. Duration 4 weeks. Concurrent medication/care: none reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (Shire Development Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE 30MG versus PLACEBO	
Protocol outcome 1: CGI at <3- or >6-months	

Study (subsidiary papers)

Adler 2008¹¹ (Mattingly 2013⁴³⁵, Adler 2009¹⁰, Kollins 2011³⁸⁰)

- Actual outcome for Adult: CGI-I: Improved or very much improved at 4 weeks; Group 1: 68/119, Group 2: 18/62; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS Total Scores (final values) adjusted at 4 weeks; Group 1: mean -16.2 (SD 11.56); n=119, Group 2: mean -8.2 (SD 11.26); n=62; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome: ADHD-RS Total Scores (final values) adjusted at 4 weeks; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Adult: Discontinuation due to adverse events at 4 weeks; Group 1: 4/119, Group 2: 1/62; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE 50MG versus PLACEBO

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Adult: CGI-I: Improved or very much improved at 4 weeks; Group 1: 73/117, Group 2: 18/62; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS Total Scores (final values) adjusted at 4 weeks; Group 1: mean -17.4 (SD 11.36); n=117, Group 2: mean -8.2 (SD 11.26); n=62; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Adult: Discontinuation due to adverse events at 4 weeks; Group 1: 8/119, Group 2: 1/62; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE 70MG versus PLACEBO

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Adult: CGI-I: Improved or very much improved at 4 weeks; Group 1: 74/122, Group 2: 18/62; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS Total Scores (final values) adjusted at 4 weeks; Group 1: mean -18.6 (SD 11.38); n=122, Group 2: mean -8.2 (SD 11.26); n=62; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

Study (subsidiary papers)	Adler 2008¹¹ (Mattingly 2013⁴³⁵, Adler 2009¹⁰, Kollins 2011³⁸⁰)
- Actual outcome for Adult: Discontinuation due to adverse events at 4 weeks; Group 1: 9/112, Group 2: 1/62; Risk of bias: Low; Indirectness of outcome: No indirectness	
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OVERALL LDX TREATMENT GROUP versus PLACEBO	
Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months	
- Actual outcome for Adult: Clinical response (defined by a 30% or more reduction in ADHD-RS-IV and a CGI rating of 1 or 2) at 4 weeks; Group 1: 244/352, Group 2: 23/62; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1 (ADHD symptoms and CGI-I): High risk of bias due to attrition Protocol outcome 2 (Dropped out due to adverse events): Low risk of attrition bias

Study	Adler 2009¹²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=442)
Countries and setting	Conducted in USA; Setting: 30 investigative sites in the US
Line of therapy	Unclear
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Met DSM-IV criteria for ADHD assessed by Conners' Adult ADHD Diagnostic Interview for ADHD, (2) met DSM-IV criteria for social anxiety disorder assessed by the Structured Clinical Interview for DSM-IV-TR Axis I disorders-research version for social anxiety disorder (3) LSAS score of at least 50 at visit 1, with no more than a 30% decrease by visit 2 (4) CGI-O-S score of 4 or greater (5) dysthymia comorbidity was also

Study	Adler 2009 ¹²
	included (6) major depressive disorder included if diagnosed 6 months before visit 1.
Exclusion criteria	(1) Lifetime diagnosis of OCD, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorders (2) current diagnosis of panic disorder, posttraumatic stress disorder, or an eating disorder within the year preceding visit 1 (3) current diagnosis of alcohol, drug misuse, or prescription medication misuse.
Recruitment/selection of patients	July 2005 to May 2007. No further details
Age, gender and ethnicity	Age - Range: 18 - 65 years. Gender (M:F): 237:205. Ethnicity: 74% Caucasian,36% unspecified
Further population details	1. ADHD subtype: All/mixed subtypes (57.2% combined, 42.8% not specified). 2. Age: Adults 18-65 years 3. At risk population: General population 4. Comorbidities: Affective disorder (86.9% generalized social anxiety disorder, 23.3% also had generalised anxiety disorder). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear). 7. Severity: Not applicable / Not stated / Unclear (CGI-S score of 4 or greater).
Extra comments	ADHD. 86.9% generalized social anxiety disorder, 23.3% also had generalised anxiety disorder
Indirectness of population	No indirectness
Interventions	(n=224) Intervention 1: CNS stimulants - Atomoxetine. Placebo given for 2 weeks (to identify and separate high placebo responders i.e. those with more than a 25% decrease in social anxiety symptoms). Atomoxetine then administered at 40mg/day for a minimum of 7 days, followed by 80mg/day (target dose) for a minimum of 7 days. At week 10, patients with significant residual symptoms could increase their dose to 100mg/day. Dose decreases were allowed, but patients were discontinued if a decrease below 40mg/day was requested. Mean final dose was 82.9mg/day (SD not specified?). Duration 16 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=218) Intervention 2: No treatment - Placebo. Placebo. Duration 16 weeks. Concurrent medication/care: not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Principal author funded by industry (Abott Laboratories, Cortex Pharmaceuticals, Bristol-Myers Squibb, Merck & Co, Eli Lilly and Company + 6 more organisations.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: AAQoL Total Change scores at 14 weeks; Group 1: mean 14.9 (SD 17.1); n=224, Group 2: mean 16.5 (SD 11.1); n=218;	

Study	Adler 2009 ¹²
	<p>AAQoL 0-100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <ul style="list-style-type: none"> - Actual outcome for Adult: AAQoL life outlook domain subscale change scores at 14 weeks; Group 1: mean 11.5 (SD 17.6); n=224, Group 2: mean 16.8 (SD 8.8); n=218; AAQOL 0-100 (if reversed and transformed) if not, 29-145 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: AAQoL life productivity domain subscale change scores at 14 weeks; Group 1: mean 17.2 (SD 21.9); n=224, Group 2: mean 20.8 (SD 12.9); n=218; AAQOL 0-100 (if reversed and transformed) if not, 29-145? Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: AAQoL psychological health domain subscale change scores at 14 weeks; Group 1: mean 15.8 (SD 21.9); n=224, Group 2: mean 20.8 (SD 11.2); n=218; AAQOL 0-100 (if reversed and transformed) if not, 29-145 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: AAQoL quality of relationships subscale change scores at 14 weeks; Group 1: mean 13.7 (SD 20.5); n=224, Group 2: mean 18.6 (SD 9.8); n=218; AAQOL 0-100 (if reversed and transformed) if not, 29-145 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: CAARS:Inv:SV Total Change Scores at 14 weeks; Group 1: mean -8.7 (SD 10); n=176, Group 2: mean -5.6 (SD 10.2); n=166; CAARS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS:Inv:SV ADHD Index Subscale Change Scores **estimated attrition and number analysed unknown (and response = inclusion criteria) at 14 weeks; Group 1: mean -5.7 (SD 7.3); n=176, Group 2: mean -3.2 (SD 6.7); n=166; CAARS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS:Inv:SV Hyperactivity/Impulsivity Subscale Change Scores **estimated attrition and number analysed unknown (and response = inclusion criteria) at 14 weeks; Group 1: mean -3.9 (SD 5.3); n=176, Group 2: mean -2 (SD 5.2); n=166; CAARS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS:Inv:SV Inattention Subscale Change Scores **estimated attrition and number analysed unknown (and response = inclusion criteria) at 14 weeks; Group 1: mean -4.8 (SD 5.7); n=176, Group 2: mean -3.6 (SD 6.2); n=166; CAARS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CGI-O-S Change Scores at 14 weeks; Group 1: mean -0.76 (SD 1.1); n=176, Group 2: mean -0.6 (SD 1); n=166; CGI-O-S 0-7 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	<p>Protocol outcome 1 (quality of life): high risk of bias due to attrition bias</p> <p>Protocol outcome 2 (ADHD symptoms): very high risk of bias due to (1) high attrition bias, that was estimated (2) selection bias; only participants that didn't respond to 2 weeks of placebo treatment were included in the</p>

Study	Adler 2009¹²
	analysis and (3) outcome reporting bias; number of participants included in the outcome was not specified. CGI-I-S: high risk of bias due to attrition bias

Study (subsidiary papers)	NCT00190736 trial: Adler 2009¹⁶ (Brown 2011¹²¹)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=206)
Countries and setting	Conducted in USA; Setting: Outpatient sites
Line of therapy	Unclear
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	DSM-IV-TR criteria for adult ADHD met. CGI-ADHD-S score of 4 or higher.
Exclusion criteria	Comorbid exclusions: current major depression or anxiety disorder, history of bipolar disorder or psychotic disorder. Failure to respond to ADHD stimulant treatment, bupropion or other non-stimulants could cause exclusion but based on clinician opinion.
Recruitment/selection of patients	Multicentre trial with patients recruited from October 2004 to May 2006.
Age, gender and ethnicity	Age - Range: Range:18-54 years. Mean age=37.6 years. Gender (M:F): 251:250. Ethnicity: 87.9% white, 12.1% unspecified
Further population details	1. ADHD subtype: All/mixed subtypes (72% combined subtype). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Mixed
Extra comments	Adult ADHD.
Indirectness of population	No indirectness
Interventions	(n=250) Intervention 1: CNS stimulants - Atomoxetine. Patients in the intervention arm began treatment with a single oral dose of 25 mg per day for a minimum of 7 days followed by 40 mg/d for another minimum 7 days. At the end of visit 3, the dosage was increased to 80 mg/d unless the increase was precluded by tolerability issues or adverse events. At the end of visit 5, the dosage could be increased to 100 mg/d dependent on continued ADHD symptoms and/or tolerability issues. Mean final dose was 84.5mg/day.

Study (subsidiary papers)	NCT00190736 trial: Adler 2009¹⁶ (Brown 2011¹²¹)
	Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration: (n=251) Intervention 2: No treatment - Placebo. No details provided. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Company)

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

Protocol outcome 1: Quality of life at <3- or >6-months

- Actual outcome: Adult ADHD quality of life scale - change score at 6 months; Group 1: mean -13.1 (SD 16.1); n=243,
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156; Group 2 Number missing: 139
- Actual outcome: Adult ADHD Self-Report (ASRS): Screening Version (change score) -Evening at 6 months; Group 1: mean -14.3 (SD 14.6); n=243, Group 2: mean -8.5 (SD 14.2); n=248; AISRS 0-54 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156; Group 2 Number missing: 139
- Actual outcome: Adult ADHD Self-Report (ASRS): Screening Version (change score) -Evening hyperactivity impulsive subscore at 6 months;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156; Group 2 Number missing: 139

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome: Adult ADHD Investigator Symptom Rating Scale-Total at 6 months; Group 1: mean -14.1 (SD 13.3); n=243, Group 2: mean -10.5 (SD 12.7); n=248; AISRS 0-54 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156, Reason: Not stated; Group 2 Number missing: 139, Reason: Not stated
- Actual outcome: Conners Adult ADHD Rating scale -Investigator rated (CAARS-Inv:SV)Evening total - change score at 6 months; Group 1: mean -7.3

Study (subsidiary papers)	NCT00190736 trial: Adler 2009 ¹⁶ (Brown 2011 ¹²¹)
	<p>(SD 8.2); n=243, Group 2: mean -5 (SD 7.3); n=248; ASRS 0-54?? Top=High is poor outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156, Reason: Not stated; Group 2 Number missing: 139, Reason: Not stated - Actual outcome: CGI ADHD scale at 6 months; Group 1: mean -1.2 (SD 1.2); n=243, Group 2: mean -0.9 (SD 1.2); n=248; CGI 0-7 Top=High is poor outcome 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: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: Unclear, Reason: Unclear - but states if any of the 9 evaluation visits were missed, this was viewed as not completing study; Group 2 Number missing: Unclear, Reason: Unclear - but states if any of the 9 evaluation visits were missed, this was viewed as not completing study - Actual outcome: AISRS hyperactive/impulsive subscale change scores at 6 months; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156; Group 2 Number missing: 139 - Actual outcome: AISRS inattention subscale change scores at 6 months; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156; Group 2 Number missing: 139 - Actual outcome: Adult ADHD Self-Report (ASRS): Screening Version (change score) -Evening inattentive subscore at 6 months; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: 156; Group 2 Number missing: 139</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome: Drop-outs due to adverse events at 6 months; Group 1: 43/250, Group 2: 14/251 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Patient characteristics and baseline symptoms measures were similar between treatment groups and similar to previous atomoxetine trial (not reported though); Group 1 Number missing: ; Group 2 Number missing: Unclear</p>
<p>Protocol outcomes not reported by the study</p>	<p>CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months</p>

Study	CR011560 trial: Adler 2009 ²¹
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	7 weeks (n=229)
Countries and setting	Conducted in USA; Setting: 27 investigative sites in the United states
Line of therapy	1st line
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic course of ADHD, AISRS score of 24 or greater, global assessment of functioning score between 41 and 60
Exclusion criteria	HAM-A score of 21 or higher, or symptoms of moderate severity of depression using HAM-D were excluded. Known non-responders were excluded. Subjects with a history of allergy to methylphenidate, any coexisting medical condition or taking medicine that could interfere. Known or suspected structural cardiac abnormality, family history of Tourette's or motor/verbal tics, history of seizure disorder, uncontrolled hyperthyroidism, other psychiatric diagnoses, suicidal ideation, history of drug or alcohol abuse in the last 6 months.
Recruitment/selection of patients	Patients that met the inclusion criteria recruited from May 2006 and November 2006.
Age, gender and ethnicity	Age - Range: 18 to 65 years. Gender (M:F): 127:99. Ethnicity: ~88% non-Hispanic, ~88% white, ~6% African American
Further population details	1. ADHD subtype: All/mixed subtypes (~80% combined type). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Extra comments	Most subjects had ADHD combined type (81% in the OROS methylphenidate,79.1% in the placebo group) rather than inattentive type or hyperactive/impulsive type. All medications taken within 30 days before the 30 days before the screening visit were recorded. During the study, all new concomitant medications were listed; 93% were not taking ADHD medication at baseline
Indirectness of population	No indirectness
Interventions	(n=113) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . All patients initiated treatment with 36 mg of OROS methylphenidate and continued with incremental increases of 18mg every 7 days until an individualised dose was achieved. This was achieved when AISRS decreased by 20% from baseline and CGI-I rating was achieved or titration to the maximum dose of 108 mg was reached. Mean final dose= 67.7mg (titration up each week). Patients

Study	CR011560 trial: Adler 2009²¹
	<p>were washed out from all ADHD medication for 7 to 14 days before treatment. Duration 7 weeks. Concurrent medication/care: All medications taken within 30 days before the 30 days before the screening visit were recorded. Subjects were washed out from all ADHD medication for 7-14 days before the beginning of the study. During the study, all new concomitant medications were listed; .93% were not taking ADHD medication at baseline</p> <p>Further details: 1. Dose: 2. Method of titration:</p> <p>(n=116) Intervention 2: No treatment - Placebo. Mean placebo equivalent dose = 86.9mg +/- 27.81. Duration 7 weeks. Concurrent medication/care: All medications taken within 30 days before the 30 days before the screening visit were recorded. During the study, all new concomitant medications were listed; .93% were not taking ADHD medication at baseline.</p> <p>Further details: 1. Dose: 2. Method of titration:</p>
Funding	Principal author funded by industry (Many companies e.g. Eli Lilly, Pfizer, also NIMH)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: Adult ADHD Investigator Symptom Report Scale lease square mean change score from baseline at 7 weeks; Group 1: mean -10.6 (SD 11.43); n=110, Group 2: mean -6.8 (SD 11.42); n=116; AISRS 0-54 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex, ADHD subscale, mean body mass index and mean global assessment of functioning scores.; Group 1 Number missing: 42/113, Reason: 16 adverse events, 8 subjects' request, 5 non-adherence, 2 other unknown reasons, 8 lost to follow up; Group 2 Number missing: 26/116, Reason: 6 adverse events, 5 subjects' request, 5 non-adherence, 6 other unknown reasons, 4 lost to follow up

- Actual outcome for Adult: Final CGI-I mean change score from baseline (adjusted for baseline variables -not listed but age, sex, body weight indices and ethnicity) at 7 weeks; Group 1: mean 3.02 (SD 1.12); n=103, Group 2: mean 3.43 (SD 1.14); n=115

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex, ADHD subscale, mean body mass index and mean global assessment of functioning scores.; Group 1 Number missing: 42/113, Reason: 16 adverse events, 8 subjects' request, 5 non-adherence, 2 other unknown reasons, 8 lost to follow up; Group 2 Number missing: 26/116, Reason: 6 adverse events, 5 subjects' request, 5 non-adherence, 6 other unknown reasons, 4 lost to follow up

- Actual outcome for Adult: Treatment response (defined as at least 30% improvement on AISRS and CGI-I score of 1 or 2) at 7 weeks;

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex, ADHD subscale, mean body mass index and mean

Study	CR011560 trial: Adler 2009²¹
<p>global assessment of functioning scores.; Group 1 Number missing: 42, Reason: 16 adverse events, 8 subjects' request, 5 non-adherence, 2 other unknown reasons, 8 lost to follow up; Group 2 Number missing: 26, Reason: 6 adverse events, 5 subjects' request, 5 non-adherence, 6 other unknown reasons, 4 lost to follow up</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Dropped out due to adverse events at 7 weeks; Group 1: 16/110, Group 2: 6/116 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 ; Baseline details: comparable for age,sex, ADHD subscale, mean body mass index and mean global assessment of functioning scores.; Group 1 Number missing: 42/113, Reason: 16 adverse events, 8 subjects' request, 5 non-adherence, 2 other unknown reasons, 8 lost to follow up; Group 2 Number missing: 26/116, Reason: 6 adverse events, 5 subjects' request, 5 non-adherence, 6 other unknown reasons, 4 lost to follow up</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Allen 2005²⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=148)
Countries and setting	Conducted in USA; Setting: 14 sites, chiefly hospitals and clinics in the US
Line of therapy	Mixed line
Duration of study	Intervention time: 18 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	All study subjects met the DSM-IV criteria for ADHD and had concurrent Tourette syndrome or chronic motor tic disorder, as diagnosed by clinical interview and examination by the investigator and confirmed by K-SADS-PL. Subjects' scores on the ADHDRS-IV-Parent Inv had to be at least 1.5 standard deviations above the age and sex norm for diagnostic subtype or for the total score for the combined subtype, using published norms for the ADHDRS-Parent:Inv at visits 1 and 2. Subjects' Yale Global Tic Severity Scale total scores had to be at least 5 at both visits 1 and 2.

Study	Allen 2005 ²⁵
Exclusion criteria	A Children's Yale-Brown Obsessive Compulsive Scale total score >15 or diagnosis of OCD severe enough to require pharmacotherapy; a Children's Depression Rating Scale-Revised total score >40 or diagnosis of depression severe enough to require pharmacotherapy; a history of bipolar disorder or psychosis; seizure disorder; or current use of any psychotropic medication other than study drug.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range: 7-17.5. Gender (M:F): 131/17. Ethnicity: 87.8% white
Further population details	1. ADHD subtype: All/mixed subtypes (60.7% Combined, 35.9% Inattentive, 3.4% Hyperactive/impulsive). 2. Age: Mixed (7-17). 3. At risk population: General population 4. Comorbidities: Mixed 5. Diagnostic method: 6. Line of treatment: 7. Severity:
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: CNS stimulants - Atomoxetine. 0.5 mg/kg/day, titrated up to 1 mg/kg/day, at visits 4 and 5 this could be titrated upward or downward or maintained within the range of 0.5 to 1.5 mg/kg/day. Duration 18 weeks. Concurrent medication/care: Psychotropic medication, other than the study drug, were not allowed at any time during the study Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=72) Intervention 2: No treatment - Placebo. No details given. Duration 18 weeks. Concurrent medication/care: Psychotropic medication, other than the study drug, were not allowed at any time during the study Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Sponsored by Eli Lilly and Company)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS total score (parent rated) at 18 weeks; Group 1: mean -10.9 (SD 10.9); n=74, Group 2: mean -4.9 (SD 10.3); n=71; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS inattentive subscale (parent rated) at 18 weeks; Group 1: mean -5.7 (SD 6.7); n=74, Group 2: mean -2.7 (SD 6.8); n=71; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS hyperactive subscale (parent rated) at 18 weeks; Group 1: mean -5.2 (SD 5.3); n=74, Group 2: mean -2.1 (SD 4.8); n=71; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

Study	Allen 2005²⁵
- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 18 weeks; Group 1: 2/76, Group 2: 1/72; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: Very high risk of bias due to attrition Protocol outcome 2: Low risk of bias

Study	Amiri 2008³⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Iran; Setting: Outpatient child and adolescent clinic at Roozbeh Psychiatric Hospital in Tehran, Iran.
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Met the DSM-IV-TR diagnostic criteria for ADHD (2) newly diagnosed (3) total and/or subscale score on ADHD-RS-IV School version at least 1.5 standard deviations above norms for patient's age and gender.
Exclusion criteria	(1) History or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric comorbidity that required pharmacotherapy (2) any evidence of suicide risk and intellectual disability (3) clinically significant chronic medical conditions (such as seizures, dependence on drugs, hyper/hypo-tension) (4) habitual consumption of more than 250 mg/day of caffeine.
Recruitment/selection of patients	Recruited from the child and adolescent clinic at Roozbeh Psychiatric Hospital
Age, gender and ethnicity	Age - Range: 16-15 years. Gender (M:F): 47:13. Ethnicity: 100% Persian
Further population details	1. ADHD subtype: Combined (100% of patients combined subtype). 2. Age: Mixed (Children and young people (6-15 years)). 3. At risk population: Not applicable / Not stated / Unclear (Not stated. Likely general population.). 4. Comorbidities: Not applicable / Not stated / Unclear (Most comorbidities excluded. No other

Study	Amiri 2008 ³⁵
	details). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: 1st line (drug naive) (All 'newly diagnosed'). 7. Severity: Not applicable / Not stated / Unclear (ADHD-RS-IV school version scores >1.5SD above norms for age and gender. Mean ADHD-RS-IV scores at baseline approximately 40 (parent) and 35 (teacher)).
Indirectness of population	No indirectness
Interventions	<p>(n=30) Intervention 1: CNS stimulants - Modafanil. 200-300 mg/day (once daily) depending on weight (200 mg/ day for <30 kg and 300 mg/day for >30 kg). modafanil was titrated up during the trial according to the following schedule: week 1 100 mg/day, week 2: 200 mg/day (capsule of modafanil in the morning and capsule of placebo in the afternoon) and week 3: 300 mg/day for children >30 kg (capsule of modafanil in the morning, capsule of placebo at midday and capsule of placebo at 16:00). Duration 6 weeks. Concurrent medication/care: not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (200-300 mg/day (once daily), depending on weight (200 mg/day for <30 kg and 300mg/day for >30 kg)).</p> <p>(n=30) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). 20-30 mg/day (once daily) depending on weight (20 mg/ day for <30 kg and 30 mg/day for >30 kg). Methylphenidate was titrated up during the trial according to the following schedule: week 1 10 mg/day (5 mg in the morning and 5 mg at midday), week 2: 20 mg/day (10 mg in the morning and 10 mg at noon) and week 3: 30 mg/day for children >30 kg (10 mg in the morning, 10 mg at midday and 10 mg at 16:00). Duration 6 weeks. Concurrent medication/care: not stated Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (20-30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg)).</p>
Funding	Academic or government funding (Tehran University of Medical Sciences)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL GROUP versus METHYLPHENIDATE GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: Parent ADHD Rating Scale at 6 weeks ; Group 1: mean -24.36 (SD 11.66); n=30, Group 2: mean -22.66 (SD 14.88); n=30; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Teacher ADHD Rating Scale at 6 weeks; Group 1: mean -20.53 (SD 6.99); n=30, Group 2: mean -21.33 (SD 12.21); n=30; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at

Study	Amiri 2008³⁵
	<3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Amiri 2012³⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Iran; Setting: Tabriz University of Medical Sciences, Department of Psychiatry
Line of therapy	1st line
Duration of study	Intervention time: 6 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult: 18-45 years
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Met DSM-IV criteria for adult ADHD (2) aged between 18-45 years
Exclusion criteria	(2) Met DSM-IV criteria for current psychiatric disorders other than adult ADHD (2) Significant chronic medical condition such as seizures or cardiovascular disease (3) history of alcohol/drug abuse or dependency within the last 6 months (4) pregnant or breastfeeding women.
Recruitment/selection of patients	The participants of the study were selected from the parents or siblings of children diagnosed with ADHD, who were referred to the Child and adolescent Psychiatry Clinic of Razi Psychiatric Hospital in Tabriz, Iran. The authors specified that this recruitment method was used due to the high familial risk for ADHD.
Age, gender and ethnicity	Age – Range: 18-45 years. Gender (M:F): 24/17. Ethnicity: not specified
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (not reported). 2. Age: Adults 18-65 years (Adults 18-45 years). 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear (Not stated. No comorbid mental health or chronic medical disease). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: 1st line (drug naïve) (100% naïve). 7. Severity: Not applicable / Not stated / Unclear (Mean = 83 and 84 on the Conners symptoms total).
Extra comments	All participants had history of childhood ADHD evaluated by the Kiddie Schedule for Affective Disorders and Schizophrenia.
Indirectness of population	No indirectness

Study	Amiri 2012 ³⁴
Interventions	<p>(n=22) Intervention 1: SNRI antidepressants - Venlafaxine. Dose of 75 mg per day for weeks 1 and 2, increased to 75 mg twice a day in weeks 3 and 4 and reaching the end-point dose of 225 mg per day in three divided doses for weeks 5 and 6. Dosing was not flexible. Duration 6 week. Concurrent medication/care: No other medication Further details: 1. Dose: Not applicable / Not stated / Unclear (75 mg per day for 2 weeks, 150 mg per day for 2 weeks, 225 mg per day for 2 weeks). 2. Method of titration: Fixed dose (All participants received same dose, titrated up in set stages).</p> <p>(n=22) Intervention 2: No treatment - Placebo. Matching Placebo (Starch) to active treatment. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration:</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VENLAFAXINE GROUP versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-ADHD symptoms total at 6 weeks; Group 1: mean 28.8 (SD 12.21); n=20, Group 2: mean 13.55 (SD 12.83); n=21; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-Inattentive symptoms at 6 weeks; Group 1: mean 25.35 (SD 1.95); n=20, Group 2: mean 14.65 (SD 12.72); n=21; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-Hyperactive/impulsive symptoms at 6 weeks; Group 1: mean 26.6 (SD 10.78); n=20, Group 2: mean 11.35 (SD 11.87); n=21; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: Conners Adult ADHD Rating Scale(Self-report)-ADHD index at 6 weeks; Group 1: mean 25.35 (SD 12.47); n=20, Group 2: mean 12.05 (SD 6.01); n=21; CAARS 0-84 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: Treatment response (defined as 25% drop in ADHD index of the CAARS) at 6 weeks; Group 1: 15/22, Group 2: 4/22; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Serious adverse events at All - Actual outcome for Adult: Serious adverse events at 6 weeks; Group 1: 0/22, Group 2: 0/22; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Drop out due to adverse events at 6 weeks; Group 1: 1/22, Group 2: 0/22; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months;

Study	Amiri 2012³⁴
study	Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Anon 2002⁶³²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=136)
Countries and setting	Conducted in USA; Setting: Universities across the USA
Line of therapy	Unclear
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) indication from a teacher that ADHD symptoms were sufficient enough for inclusion (rated as "pretty much" or "very much" in the classroom setting using the Disruptive behaviour disorders rating scale) (2) severity of ADHD rated above specified cut off scores on the IOW conners teacher rating scale(boys in grade 2-3 = 10, grade 4 and above = 9; girls in grade 2-3 = 7, grade 4 and above =6) (3) CGAS score of 70 or more (4) DSM-IV criteria for Tourette disorder, chronic motor tic disorder, or chronic vocal tic disorder
Exclusion criteria	(1) evidence of a secondary tic disorder such as tardive tics or Huntington disease (2) major depression, PDD, autism, psychosis, intellectual disability, anorexia nervosa or bulimia, a serious cardiovascular disorder, impaired renal function or pregnancy (3) any ECG abnormalities (4) family history of cardiac problems or premature sudden death, history of syncope (5) blood pressure less than 2 SDs from the age and gender adjusted mean
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 7 to 14 years. Gender (M:F): 108:28. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (70% inattentive, 2% hyperactive impulsive, 28% combined). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Tic disorder and Tourette's (95% Tourette's, 4% CMTD, 1% CVTD). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (58% had prior stimulant use and 36% prior use of clonidine). 7. Severity: Moderate (See inclusion criteria).

Study	Anon 2002 ⁶³²
Indirectness of population	No indirectness
Interventions	<p>(n=37) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). 4 week titration individualised per participant in order to reach optimal dosages, which was defined as reaching a level of school functioning considered good, with no further room for improvement and an acceptable level of side effects. An 8 week maintenance dosage period followed, during the first 6 weeks dosage changes were permitted in cases of side effects. Duration 16 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed (Mean 25.7mg/day). 2. Method of titration: Titrated to optimum dose</p> <p>(n=34) Intervention 2: Clonidine. 4 week titration individualised per participant in order to reach optimal dosages, which was defined as reaching a level of school functioning considered good, with no further room for improvement and an acceptable level of side effects. An 8 week maintenance dosage period followed, during the first 6 weeks dosage changes were permitted in cases of side effects. Duration 16 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed (0.25mg per day mean). 2. Method of titration: Titrated to optimum dose</p> <p>(n=33) Intervention 3: Combination - See description. Combination of MPH and clonidine. 4 week titration of clonidine was followed by a 4 week titration of MPH, both individualised per participant in order to reach optimal dosages, which was defined as reaching a level of school functioning considered good, with no further room for improvement and an acceptable level of side effects. An 8 week maintenance dosage period followed, during the first 6 weeks dosage changes were permitted in cases of side effects. Duration 12 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed (Clonidine mean 0.25mg/day and 26.1mg per day MPH). 2. Method of titration: Titrated to optimum dose</p> <p>(n=32) Intervention 4: No treatment - Placebo. Placebo. Duration 16 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:</p>
Funding	Academic or government funding (NIC, GCRC and Tourette Syndrome Association)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus CLONIDINE</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,</p>	

Study	Anon 2002 ⁶³²
	<p>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4 - Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7 - Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7 - Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE AND METHYLPHENIDATE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ASQ teacher total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7 - Actual outcome for Children (up to 18 years): ASQ parent total scores at 12 weeks; Mean; ; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 7</p>
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months;

Study	Anon 2002 ⁶³²
study	Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Arabgol 2015 ⁴¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in Iran; Setting: Hospital. No further details
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis by two psychiatrists. No further details
Exclusion criteria	The presence of any physical condition, intellectual disability or any psychiatric comorbid disorders except conduct disorder and oppositional defiant disorder.
Recruitment/selection of patients	Allocation of outpatients by the resident of paediatric psychiatry of Imam Hossein Hospital. No further details
Age, gender and ethnicity	Age - Range: 3 to 6 years. Gender (M:F): 27:11. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (57.57% combined, 33.33% hyperactive/impulsive, 9.09% inattentive). 2. Age: Pre-schoolers (<6 years) (3-6 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated, probable general population). 4. Comorbidities: Not applicable / Not stated / Unclear (Most comorbidities excluded, except ODD and conduct disorder (N not reported)). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: Not applicable / Not stated / Unclear (Not stated. All new patients with no drug history in the 2 weeks before the study). 7. Severity: Not applicable / Not stated / Unclear (Total mean baseline scores parent ADHD-RS approximately 28).
Extra comments	ADHD
Indirectness of population	No indirectness

Study	Arabgol 2015 ⁴¹
Interventions	<p>(n=18) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Dose started at 2.5 mg per day and increased every week based on therapeutic response and the patient's tolerance. The optimal dose of methylphenidate was 20 mg/day in two divided doses. The dose was chosen according to prior studies. The mean dose was 12.83 +/- 0.56 mg/day. Duration 6 weeks. Concurrent medication/care: New patients with no drug history. No other drugs or psychological interventions allowed during the intervention stage Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (Started at 2.5 mg/day and gradually increased based on the therapeutic response and patients tolerance).</p> <p>(n=20) Intervention 2: Antipsychotics - Risperidone. Starting dose of 0.25 mg per day in one dose, increased each week based on therapeutic response and patient's tolerance. The optimal dose was 2mg/day in two divided doses. The mean daily dose at the end of the 6 weeks was 0.89 +/- 0.48 mg/day. Dosage chosen according to effective dosing in previous studies. Duration 6 weeks. Concurrent medication/care: New patients with no drug history. No other drugs or psychological interventions allowed during the intervention stage Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (Started at 0.25 mg/day and gradually increased based on therapeutic response and the patient's tolerance).</p>
Funding	Academic or government funding (Behavioral Sciences Research Center (Shahid Beheshti Medical University))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus RISPERIDONE

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Parent ADHD Rating Scale Total Scores (final values) at 6 weeks; Group 1: mean 15.53 (SD 6.3); n=15, Group 2: mean 16.64 (SD 9.53); n=18; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Parent ADHD Rating Scale Inattentive Scores (final values) at 6 weeks; Group 1: mean 6.84 (SD 3.64); n=15, Group 2: mean 7.58 (SD 4.5); n=18; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Parent ADHD Rating Scale hyperactive/impulsive Scores (final values) at 6 weeks; Group 1: mean 8.69 (SD 4.21); n=15, Group 2: mean 9 (SD 5.97); n=18; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Conners Parent Rating Scale- Revised total scores (final values) at 6 weeks; Group 1: mean 31.69 (SD 18.43); n=15, Group 2: mean 30.76 (SD 19.2); n=18; CPRS-R 0-81? Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Arabgol 2015 ⁴¹
Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to side effects at 6 weeks; Group 1: 3/18, Group 2: 2/20; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: (ADHD symptoms): high risk of attrition bias Protocol outcome 2: (Dropped out due to adverse events): low risk of bias

Study	Arnold 2006 ⁴⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in USA
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV evaluation by a child and adolescent psychiatrist
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 5-15. Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) (Mean(SD): 9.26(2.93)). 3. At risk population: General population 4. Comorbidities: ASD (43.8%). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness

Study	Arnold 2006 ⁴⁵
Interventions	<p>(n=16) Intervention 1: CNS stimulants - Atomoxetine. Atomoxetine was given as split doses, morning and afternoon, starting at 0.25mg/kg/day and increased every 4-5 days by increments of 0.3 to 0.4 mg/kg/day. The max daily dose was 1.4mg/kg/day, not to exceed 100mg/day. For subjects also taking a significant CYP2D6 inhibitor, the dose increments were 0.2 to 0.3 mg/kg/day and dose was capped at 1.2 mg/kg/day. Duration 6 weeks. Concurrent medication/care: Concomitant medications other than systemic catecholaminergic drugs and beta-blockers were allowed if the dose was stable for 1 month before entry Further details: 1. Dose: 2. Method of titration: Titrated to optimum dose</p> <p>(n=16) Intervention 2: No treatment - Placebo. No treatment. Duration 6 weeks. Concurrent medication/care: Concomitant medications other than catecholaminergic drugs and beta-blockers were allowed if the dose had been stable for 1 month prior to entry Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Lilly, Shire, Janssen and PediaMed)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): DSM-IV Hyperactive subscale - Parent rated at 6 weeks; Group 1: mean 10.4 (SD 6.88); n=16, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): DSM-IV Inattentive subscale - Parent rated at 6 weeks; Group 1: mean 11.2 (SD 5.53); n=16, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Treatment response (defined as CGI-I of 1 or 2 and 25% improvement on ABC-H) at 6 weeks; Group 1: 9/16, Group 2: 4/16; Risk of bias: High; Indirectness of outcome:</p> <p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Aberrant Behaviour Checklist Hyperactivity subscale at 6 weeks; Group 1: mean 19.31 (SD 13.42); n=16, Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1 (ADHD symptoms): DSM-IV outcomes: very high risk of bias due to (1) high risk of attrition bias, and (2) high risk of

Study	Arnold 2006 ⁴⁵
	measurement bias; it is unclear if a validated scale was used CGI-I: high risk of attrition bias Protocol outcome 2 (Behavioural outcomes): high risk of attrition bias.

Study	Arnold 2014 ⁵⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=338)
Countries and setting	Conducted in USA; Setting: 18 medical centers in the US
Line of therapy	1st line
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	patients included if they met DSM-IV criteria for ADHD(combined, predominantly inattentive or predominantly hyperactive-impulsive subtype) for which symptoms were present before the age of 7 years and persisted for at least the prior 6 months, according to a psychiatric/clinical evaluation using the CDS. Patients on medication had to discontinue use of all medication for ADHD- washout was a minimum of 7 days after the last dose. Subjects were also required to have HAM-A and HAM-D score <15, and an AISRS total score of >24. In addition, a CGI-S rating of ADHD>4 was required for study entry
Exclusion criteria	History or current diagnosis of schizophrenia, bipolar disorder, or other psychotic disorders, suicidal ideation, history of suicide attempts, or a clinical assessment of suicide risk. Any acute psychiatric comorbidity that required pharmacotherapy was grounds for exclusion of the study as well as significant sleep disorder, use of any antidepressant within 2 weeks before baseline and drug or alcohol dependence in the last 6 months
Recruitment/selection of patients	From May 2006 to January 2007. No further details
Age, gender and ethnicity	Age - Mean (SD): 39.3(11.49). Gender (M:F): Define. Ethnicity: 87% White, 5% Black, 2% Asian, less than

Study	Arnold 2014 ⁵⁰
	1% American Indian or Alaskan native, less than 1% Pacific Islander, 5% unspecified. (Also - 8% Hispanic or Latino)
Further population details	1. ADHD subtype: All/mixed subtypes (percentages not specified). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) (Majority first line). 7. Severity: Moderate
Extra comments	ADH
Indirectness of population	No indirectness
Interventions	<p>(n=73) Intervention 1: CNS stimulants - Modafanil. Patients were instructed to take 6 tablets orally, once daily in the morning. The study drug was titrated from 85mg/day during the first 3 weeks, up to the assigned dosage. Duration 9 weeks. Concurrent medication/care: 32% had received ADHD medication within the past 5 years Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=73) Intervention 2: CNS stimulants - Modafanil. Patients were instructed to take 6 tablets orally, once daily in the morning. The study drug was titrated from 85mg/day during the first 3 weeks, up to the assigned dosage. Duration 9 weeks. Concurrent medication/care: 27% had received ADHD medication within the past 5 years Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=74) Intervention 3: CNS stimulants - Modafanil. Patients were instructed to take 6 tablets orally, once daily in the morning. The study drug was titrated from 85mg/day during the first 3 weeks, up to the assigned dosage. Duration 9 weeks. Concurrent medication/care: 45% had received ADHD medication within the past 5 years Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=44) Intervention 4: CNS stimulants - Modafanil. Patients were instructed to take 6 tablets orally, once daily in the morning. The study drug was titrated from 85mg/day during the first 3 weeks, up to the assigned dosage. Randomisation broken, 510mg discontinued - manufacturer decision to stop producing 510mg tablets. Duration 9 weeks. Concurrent medication/care: 45% had received ADHD medication within the past 5 years Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=74) Intervention 5: No treatment - Placebo. Placebo. No details. Duration 9 weeks. Concurrent medication/care: 39% received ADHD medication within the past 5 years Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not</p>

Study	Arnold 2014 ⁵⁰
	stated / Unclear
Funding	Study funded by industry (Cephalon Inc (now owned by Teva Pharmaceuticals Industries Ltd))
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 255MG/DAY versus PLACEBO</p> <p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form, Change scores at < 3 months (9 weeks); Group 1: mean 5.2 (SD 7.57); n=43, Group 2: mean 4.4 (SD 8.64); n=51; Q-LES-Q-SF 14-70 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Adult ADHD Self-Report Scale Change Scores at < 3 months (9 weeks); Group 1: mean -13.7 (SD 14.54); n=43, Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Behaviour Rating Inventory of Executive Function - Adult Version Change Scores at < 3 months (9 weeks); Group 1: mean -9.2 (SD 11.36); n=42, Group 2: mean -8.1 (SD 12.61); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at < 3 months (9 weeks); Group 1: 19/73, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 340MG/DAY versus PLACEBO</p> <p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form, Change scores at < 3 months (9 weeks); Group 1: mean 5.9 (SD 10.09); n=37, Group 2: mean 4.4 (SD 8.64); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Adult ADHD Self-Report Scale Change Scores at < 3 months (9 weeks); Group 1: mean -18.6 (SD 16.89); n=37, Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Behaviour Rating Inventory of Executive Function - Adult Version Change Scores at < 3 months (9 weeks); Group 1: mean -14.9 (SD 15.07); n=37, Group 2: mean -8.1 (SD 12.61); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	

Study	Arnold 2014 ⁵⁰
<p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at < 3 months (9 weeks); Group 1: 19/73, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 425MG/DAY versus PLACEBO</p>	
<p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form, Change scores at < 3 months (9 weeks); Group 1: mean 7.4 (SD 7.05); n=39, Group 2: mean 4.4 (SD 8.64); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Adult ADHD Self-Report Scale Change Scores at < 3 months (9 weeks); Group 1: mean -17.3 (SD 13.34); n=39, Group 2: mean -12.2 (SD 14); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Behaviour Rating Inventory of Executive Function - Adult Version Change Scores at < 3 months (9 weeks); Group 1: mean -13 (SD 14.02); n=39, Group 2: mean -8.1 (SD 12.61); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at < 3 months (9 weeks); Group 1: 22/74, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL 510MG/DAY versus PLACEBO</p>	
<p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form, Change scores at < 3 months (9 weeks); Group 1: mean 3.9 (SD 7.36); n=23, Group 2: mean 4.4 (SD 8.64); n=51; Q-LES-Q 14 - 70 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Adult ADHD Self-Report Scale Change Scores at < 3 months (9 weeks); Group 1: mean -10.6 (SD 13.76); n=41, Group 2: mean -13.1 (SD 15.03); n=72; AISRS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Behaviour Rating Inventory of Executive Function - Adult Version Change Scores at < 3 months (9 weeks); Group 1: mean -6 (SD 13.48); n=23, Group 2: mean -8.1 (SD 12.61); n=51; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	

Study	Arnold 2014 ⁵⁰
Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at < 3 months (9 weeks); Group 1: 9/44, Group 2: 6/74; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcomes 1-3: Very high risk of bias Protocol outcome 4: High risk of bias

Study	Bangs 2007 ⁶²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=142)
Countries and setting	Conducted in USA; Setting: 16 investigative sites in the US
Line of therapy	1st line
Duration of study	Intervention time: Approx 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable:
Inclusion criteria	ADHD-RS-IV score at least 1.5 standard deviations above age and sex norms and a Children's Depression Rating Scale-Revised total score of 40 or more at every visit prior to randomization.
Exclusion criteria	Patients beginning structured psychotherapy for ADHD or depression less than 1 month before the trial
Recruitment/selection of patients	From July 2002 to May 2004. No further details
Age, gender and ethnicity	Age - Range: 12 to 18 years. Gender (M:F): 104:38. Ethnicity: 83% Caucasian, 17% unspecified
Further population details	1. ADHD subtype: All/mixed subtypes (43% combined, 47% inattentive, 10% is hyperactive-impulsive). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Mixed line (including drug naive) (20% were stimulant naive). 7. Severity:
Extra comments	ADHD and major depression

Study	Bangs 2007 ⁶²
Indirectness of population	No indirectness
Interventions	<p>(n=72) Intervention 1: CNS stimulants - Atomoxetine. 2 week screening and baseline assessment phase followed by a 1 week placebo lead in phase (visits 3 -4), an approximately 9 week double blind acute treatment phase and a 9 month open label treatment phase. At visit 4, patients were administered with atomoxetine, in once daily doses. The target dose was 1.2mg/kg per day which could be increased to 1.8mg/kg per day for patients with an inadequate response. Final mean daily dose of 1.51 +/-0.24mg/kg per day. Duration 10 weeks. Concurrent medication/care: No psychotropic drugs were allowed. Drugs that inhibit the CYP2D6 enzyme pathway were not allowed because of interactions with atomoxetine. Methylphenidate or other stimulants for ADHD could be continued up to 1 day prior to visit 3. 79.2% had prior stimulant exposure Further details: 1. Dose: 2. Method of titration:</p> <p>(n=70) Intervention 2: No treatment - Placebo. Placebo. Duration 10 weeks. Concurrent medication/care: No psychotropic drugs were allowed. Drugs that inhibit the CYP2D6 enzyme pathway were not allowed because of interactions with atomoxetine. Methylphenidate or other stimulants for ADHD could be continued up to 1 day prior to visit 3. 79.2% had prior stimulant exposure Further details: 1. Dose: 2. Method of titration:</p>
Funding	Principal author funded by industry (Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv at 9 weeks; Group 1: mean -13.3 (SD 10); n=71, Group 2: mean -5.2 (SD 9.9); n=70; ADHDRS-IV-Parent:Inv 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CDRS-R at 9 weeks; Group 1: mean 53.4 (SD 10.9); n=71, Group 2: mean -12.8 (SD 10.4); n=70; Children's depression rating scale-revised 0-63? Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CGI-I responders at 9 weeks; Group 1: 33/69, Group 2: 12/67; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): discontinued due to adverse events at 9 weeks; Group 1: 1/72, Group 2: 1/70; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic

Study	Bangs 2007 ⁶²
study	outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Barrickman 1995 ⁶⁷
Study type	RCT (Patient randomised; Crossover: 14 days)
Number of studies (number of participants)	(n=18)
Countries and setting	Conducted in USA; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not specified
Exclusion criteria	IQ <70 and any other major Axis I,II or III diagnoses. a seizure history, eating disorders and use of MAOI
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 7 to 17 years. Gender (M:F): Define. Ethnicity: 100% white
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (5 drug naive, 10 previously treated with methylphenidate). 7. Severity: Mixed (12 rated as severe and 3 as moderate (on CGI)).
Extra comments	ADHD. 14 day washout of other drugs
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . 0.4mg/kg per day in the first week and titrated up to the maximum effective dosage in the following 2 weeks, to a fixed dose for the last 3 weeks. All subjects received 3 capsules per day (morning, afternoon and evening). Final mean dose 31 (11)mg per day. Duration 6 weeks. Concurrent medication/care: Other drugs washed out Further details: 1. Dose: 2. Method of titration:

Study	Barrickman 1995⁶⁷
	(n=15) Intervention 2: Bupropion. 1.5mg/kg per day in the first week, 2mg/kg per day in the second week, titrated to a final dose in the third week and fixed. Final mean dose 140 (146)mg per day (range of 50 to 200mg/day). Duration 6 weeks. Concurrent medication/care: Other drugs washed out Further details: 1. Dose: 2. Method of titration:
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): IOWA Conners rating scale (parents) total at 6 weeks; Group 1: mean 12.7 (SD 5.1); n=15, Group 2: mean 9.7 (SD 5.4); n=15; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): IOWA Conners rating scale (teacher) total at 6 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): IOWA Conners rating scale (parent+teacher) attention subscale at 6 weeks; Group 1: mean 6.8 (SD 2.5); n=15, Group 2: mean 4.4 (SD 2.1); n=15; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): IOWA Conners rating scale (parent+teacher) conduct subscale at 6 weeks; Group 1: mean 5.6 (SD 3.4); n=15, Group 2: mean 5.1 (SD 3.8); n=15; Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 6 weeks; Group 1: 0/15, Group 2: 0/15; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: high risk of attrition bias Protocol outcome 2: low risk of bias

Study	Biederman 2006⁹⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=248)

Study	Biederman 2006 ⁹⁵
Countries and setting	Conducted in USA; Setting: 28 centres in the US
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) height and weight corresponding to greater than the fifth percentile in standardized growth charts (2) stimulant naive or had manifested an unsatisfactory response to stimulant therapy (3) IQ of at least 80 (4) score of 80 or higher on the screening version of the WIAT (5) CGI-S score of 4 or more
Exclusion criteria	(1) active clinically significant GI, cardiovascular, hepatic, renal, hematologic, neoplastic, endocrine, neurologic, immunodeficiency, pulmonary or other major clinically significant disorder or disease that requires medication (2) any current psychiatric comorbidity (3) use of any prescription or non-prescription medication with psychoactive properties within 1 week of the study (4) history or evidence of substance abuse
Recruitment/selection of patients	Between February 2002 and May 2002
Age, gender and ethnicity	Age - Range: 6 to 13 years. Gender (M:F): 185:63. Ethnicity: 80% White, 20% not specified
Further population details	1. ADHD subtype: All/mixed subtypes (80% combined; 17% inattentive; 3% hyperactive impulsive). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (Drug naive and those non-responsive to other treatment). 7. Severity: Not applicable / Not stated / Unclear (CGI-S score of 4 or more).
Indirectness of population	No indirectness
Interventions	(n=197) Intervention 1: CNS stimulants - Modafanil. Children were instructed to take 3 tablets in the early morning and 2 tablets 4 to 5 hours later. Following a 7 to 10 play placebo run in phase. They were randomised to receive 300mg in the morning, 100mg in the morning followed by 200mg, or 200mg in the morning followed by 100mg. This was stratified by weight. In those less than 30kg, they were also randomised to a higher dose of 200mg in the morning followed by 200mg later. Doses were increased gradually according to the following schedule: 100mg on days 1 to 3; thereafter daily doses increased by 100mg increments until target dose was reached. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose (Titrated to fixed dose).

Study	Biederman 2006⁹⁵
	(n=51) Intervention 2: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Cephalon Inc, Frazer)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Treatment response (CGI-I score of 1 or 2) at 4 weeks; Group 1: 45/147, Group 2: 9/51 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 6</p> <p>Protocol outcome 2: Serious adverse events at All - Actual outcome for Children (up to 18 years): Serious adverse events at 4 weeks; Group 1: 0/197, Group 2: 0/51 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 6</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 4 weeks; Group 1: 9/197, Group 2: 0/51 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 22; Group 2 Number missing: 6</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Biederman 2006⁹⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=149)
Countries and setting	Conducted in USA; Setting: Psychiatry Service Massachusetts General Hospital and Department of Psychiatry, Harvard Medical School
Line of therapy	Unclear

Study	Biederman 2006 ⁹⁰
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview by age 7 as well in the last month. patients treated for anxiety disorders and depression who were receiving a stable medication regimen for at least 3 months and who had disorder specific CGI severity score of 3 or less (mildly ill) were included.
Exclusion criteria	patients with clinically significant chronic medical conditions, abnormal baseline laboratory values; IQ <80, clinically unstable psychiatric conditions (bipolar disorder, psychosis, suicidality, drug or alcohol abuse, previous adequate trial of MPH. Pregnant and nursing women were excluded also
Recruitment/selection of patients	outpatient adults with ADHD aged between 19 and 60 years
Age, gender and ethnicity	Age - Range: 19-60 years. Gender (M:F): 73:76. Ethnicity: not stated
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (unclear/not stated). 2. Age: Adults 18-65 years) (19-60 years). 3. At risk population: General population 4. Comorbidities: Mixed (Lifetime psychiatric comorbidity (including major depression, bipolar disorder, multiple anxiety disorders, ASPD and conduct disorder) 38.3%, Substance use disorder (59.6%)). 5. Diagnostic method: DSM (On the basis of clinical assessment and confirmation by structured diagnostic interview). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Extra comments	ADHD sub-type not defined. 38% of the study population had a lifetime psychiatric comorbidity. 5% suffered from major depression, 4.2% from bipolar disorder, 21% from multiple (>) anxiety disorder, 9% from ASPD, and 14% had conduct disorder. Nearly 60% had a substance use disorder of which 56% suffered from alcohol abuse/dependence and 21% from drug abuse/disorder
Indirectness of population	No indirectness
Interventions	(n=72) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Medication was titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg). During titration to optimal dose, dose was increased by 36 mg/day but only for subjects who failed to attain a priori definition of improvement (CGI improvement of 1 or 2 or a reduction in the AISRS score greater than 30%) and who did not experience adverse events. All doses of OROS MPH and placebo were delivered in identical tablets. Duration 6 weeks. Concurrent medication/care: Subjects receiving stable doses of non-monoamine oxidase inhibitor antidepressants or benzodiazepines for more than 3 months were eligible for study

Study	Biederman 2006⁹⁰
	Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=77) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: Subjects receiving stable doses of non-monoamine oxidase inhibitor antidepressants or benzodiazepines for more than 3 months were eligible for study Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Study supported by funding from the National Institute of Mental Health (NIMH) and Novartis Pharmaceuticals also supported a portion of the cost. Authors also received grant support from NIMH)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH GROUP versus PLACEBO GROUP	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Treatment response at 6 weeks; Group 1: 44/67, Group 2: 23/74; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinued due to adverse events at 6 weeks; Group 1: 9/72, Group 2: 3/77; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: Very high risk of attrition bias Protocol outcome 2: Low risk of bias

Study (subsidiary papers)	Biederman 2007⁸⁷ (Childress 2014¹⁵⁵, Lopez 2008⁴¹⁷)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=290)
Countries and setting	Conducted in USA; Setting: 40 centres across the US
Line of therapy	Mixed line

Study (subsidiary papers)	Biederman 2007 ⁸⁷ (Childress 2014 ¹⁵⁵ , Lopez 2008 ⁴¹⁷)
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants met DSM-IV-TR criteria for primary diagnosis of ADHD, combined or hyperactive-impulsive subtypes only were recruited by invitation to those patients known to the centres irrespective of current ADHD medication status. Children with an ADHD Rating Scale of (ADHD-RS-IV) score >28 were eligible. To determine if enrolment criteria were met, psychiatric evaluation was conducted using two interviews with their parents and guardians. Absence of a history of or current medical condition or use of medications that might confound results of the study also formed inclusion criteria
Exclusion criteria	Comorbid psychiatric diagnosis, history of seizures or current diagnosis of Tourette's disorder, obesity based on the investigators opinion, positive screening for illicit drug use.
Recruitment/selection of patients	Participants were recruited by invitation to those patients known to the centres irrespective of current ADHD medication status. The intention of the study was to enrol children who were not adequately treated with their current medication for ADHD or had not previously been treated for ADHD. The decision of enrolling a child was made by the individual investigator. One week of screening, one week of washout of current psychoactive medications
Age, gender and ethnicity	Age - Mean (SD): 9 (1.8) range =6-12 years. Gender (M:F): 201/89. Ethnicity: 53.4% white, 2.4% black, 16.6% Hispanic, 0.69% native American, 1.03% Asian, 0.34% native Hawaiian and 3.8% other
Further population details	1. ADHD subtype: All/mixed subtypes (96% of the study population were of the combined subtype of ADHD and 4% were of the hyperactive). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Mixed line (including drug naive) (64.5% of the study population had no previous therapy for ADHD in the past 12 months). 7. Severity:
Extra comments	96% of the study population were of the combined subtype of ADHD and 4% were of the hyperactive subtype. Co-morbid conditions not reported and formed an exclusion criteria
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Oral capsules of LDX 30 mg. No other details provided. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration: (n=74) Intervention 2: CNS stimulants - Lisdexamfetamine dimesylate. 50 Mg oral capsules of LDX (30 mg/d for week 1, with forced dose escalation to 50 mg/d for week 2-4. Median of daily dosing time was

Study (subsidiary papers)	Biederman 2007 ⁸⁷ (Childress 2014 ¹⁵⁵ , Lopez 2008 ⁴¹⁷)
	<p>reportedly in the range of 7:30 am to 6 am among the 4 treatment groups across 4 weeks No other details reported. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=73) Intervention 3: CNS stimulants - Lisdexamfetamine dimesylate. 70 Mg oral capsules of LDX (30 mg/d for week 1, with forced dose escalation to 50 mg/d for week 2 and 70 mg/d for weeks 3 and 4. Median of daily dosing time was reportedly in the range of 7:30 am to 6 am among the 4 treatment groups across 4 weeks. No other details reported. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=72) Intervention 4: No treatment - Placebo. Matching placebo capsules. Median of daily dosing time was reportedly in the range of 7:30 am to 6 am among the 4 treatment groups across 4 weeks. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=218) Intervention 5: CNS stimulants - Lisdexamfetamine dimesylate. All LDX groups combined. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p>
Funding	Funding not stated

60

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALL LDX GROUPS COMBINED versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Conners Parent Rating Scale, Revised Short Version (CPRS-R:S) Total (Least Square mean percent changes)-6 pm at 4 weeks; Group 1: mean -45.3 (SD 45.77); n=60, Group 2: mean -1.7 (SD 43.27); n=54

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 ; Baseline details: comparable for age, sex, race, diagnosis, duration of disease, age at onset of ADHD; Group 1 Number missing: 42, Reason: adverse events, loss to follow-up and lack of efficacy; Group 2 Number missing: 18, Reason: adverse events, loss to follow-up and lack of efficacy, protocol violations

- Actual outcome for Children (up to 18 years): Conners Parent Rating Scale, Revised Short Version (CPRS-R:S) ADHD Index-(Least Square mean percent changes)-6 pm at 4 weeks; Group 1: mean -46 (SD 45.77); n=218, Group 2: mean -1.9 (SD 43.27); n=72

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 ; Baseline details: comparable for age, sex, race, diagnosis, duration of disease, age at onset of ADHD; Group 1 Number missing: 42, Reason: adverse events, loss to follow-up and lack of efficacy; Group 2 Number missing: 18, Reason:

Study (subsidiary papers)	Biederman 2007 ⁸⁷ (Childress 2014 ¹⁵⁵ , Lopez 2008 ⁴¹⁷)
	<p>adverse events, loss to follow-up and lack of efficacy, protocol violations</p> <p>- Actual outcome for Children (up to 18 years): Conners Parent Rating Scale, Revised Short Version (CPRS-R:S) Hyperactivity (Least Square mean percent changes)-6 pm at 4 weeks; Group 1: mean -54.7 (SD 67.92); n=176, Group 2: mean 11.4 (SD 63.64); n=54</p> <p>Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): Conners Parent Rating Scale, Revised Short Version (CPRS-R:S) Oppositional (Least Square mean percent changes)-6 pm - behavioural outcome? at 4 weeks;</p> <p>Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Biederman 2008 ⁸⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=345)
Countries and setting	Conducted in USA; Setting: Multicentre study conducted at 48 centres in the USA
Line of therapy	Unclear
Duration of study	Intervention time: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DMS-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were 6-17 years old and met DSM-IV criteria for a primary diagnosis of ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype were eligible to participate. They were required to function intellectually at age appropriate levels; have electrocardiogram results within reference range; and have blood pressure measurements within the 95th percentile for their age, gender and height.
Exclusion criteria	Current, uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms, such as any severe comorbid Axis II disorder or severe Axis I disorder, or when other symptomatic manifestations would, in the opinion of the examining physician, contraindicate GXR treatment or confound efficacy or safety assessments. Patients who weighed <55 lb or were morbidly overweight or obese, pregnant, lactating, or hypertensive were not enrolled when they had any of the following: a QTc interval of

Study	Biederman 2008 ⁸⁹
	<p>>440 milliseconds; a history of seizure during the past two years (exclusive of febrile seizures); a tic disorder; family history of Tourette's disorder; a positive urine drug screen; any abnormal thyroid function that was not adequately treated; or any cardiac condition or family history of cardiac condition that, in the opinion of the physician investigator, would require exclusion. Patients who had taken an investigational drug within 28 days, were taking medication that affect BP or heart rate, or were taking other medication that have central nervous system effects or affect performance were also not eligible to participate.</p>
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range: 6-17. Gender (M:F): 257/88. Ethnicity: White 70.1%, Black 13.3%, Hispanic 9.9%, Asian or Pacific Islander 0.6%, Native American 0.3%, Other 5.8%
Further population details	<p>1. ADHD subtype: All/mixed subtypes (Inattentive 26.1%, Hyperactive-impulsive 2%, Combined 71.9%). 2. Age: Mixed (Children 76.8%, Young people 23.2%). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear</p>
Indirectness of population	No indirectness
Interventions	<p>(n=87) Intervention 1: Guanfacine. Patients were randomly assigned to 1 of 3 groups of GXR treatment or placebo. All patients who received GXR began dosing at 1mg/day. GXR dosages were escalated weekly in 1mg increments beginning at 1mg/day at week 1 of the double blind treatment period with the highest dosages given during weeks 4 and 5. Duration 5 weeks. Concurrent medication/care: After a screening period patients underwent a washout of approximately one week or five times the half-life of their medication. Further details: 1. Dose: 2. Method of titration: Fixed dose (Titrated to allocated dose).</p> <p>(n=86) Intervention 2: No treatment - Placebo. dose/quantity, brand name, extra details. Duration 5 weeks. Concurrent medication/care: After a screening period patients underwent a washout of approximately one week or five times the half-life of their medication. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=86) Intervention 3: Guanfacine. Patients were randomly assigned to 1 of 3 groups of GXR treatment or placebo. All patients who received GXR began dosing at 1mg/day. GXR dosages were escalated weekly in 1mg increments beginning at 1mg/day at week 1 of the double blind treatment period with the highest dosages given during weeks 4 and 5. Duration 5 weeks. Concurrent medication/care: After a screening period patients underwent a washout of approximately one week or five times the half-life of their medication. Further details: 1. Dose: 2. Method of titration: Fixed dose (Titrated to fixed dose).</p> <p>(n=86) Intervention 4: Guanfacine. Patients were randomly assigned to 1 of 3 groups of GXR treatment or placebo. All patients who received GXR began dosing at 1mg/day. GXR dosages were escalated weekly in</p>

Study	Biederman 2008 ⁸⁹
	1mg increments beginning at 1mg/day at week 1 of the double blind treatment period with the highest dosages given during weeks 4 and 5. Duration 5 weeks. Concurrent medication/care: After a screening period patients underwent a washout of approximately one week or five times the half-life of their medication. Further details: 1. Dose: 2. Method of titration: Fixed dose (Titrated to fixed dose).
Funding	Principal author funded by industry (Dr Biederman received research support from various companies)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE 2MG versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-I at 5 weeks; Group 1: 49/87, Group 2: 22/86; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV at 5 weeks; Mean -7.7 (95%CI -3.15 to -12.25) (p-value 0.0002) ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R at 5 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CTRS-R at 5 weeks; Mean -11.57 (95%CI -5.95 to -17.19) (p-value <0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Significant improvement in Parents Global Assessment at 5 weeks; Group 1: 54/87, Group 2: 20/86; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 5 weeks; Group 1: 1/87, Group 2: 1/86; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE 3MG versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-I at 5 weeks; Group 1: 43/86, Group 2: 22/86; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV at 5 weeks; Mean -7.95 (95%CI -3.4 to -12.5) (p-value 0.0001) ADHD-RS-IV 0-54 Top=High</p>	

Study	Biederman 2008 ⁸⁹
	<p>is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): CPRS-R at 5 weeks; Mean -7.36 (95%CI -0.77 to -13.95) (p-value 0.0242); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CTRS-R at 5 weeks; Mean -13.48 (95%CI -7.69 to -19.26) (p-value <0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Significant improvement in Parents Global Assessment at 5 weeks; Group 1: 44/86, Group 2: 20/86; Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 5 weeks; Group 1: 2/86, Group 2: 1/86; Risk of bias: Low; Indirectness of outcome: No indirectness <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE 4MG versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): CGI-I at 5 weeks; Group 1: 48/86, Group 2: 22/86; Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS-IV at 5 weeks; Mean -10.39 (95%CI -5.82 to -14.97) (p-value <0.0001) ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R at 5 weeks; Mean -12.70 (95%CI -6.11 to -19.31) (p-value <0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CTRS-R at 5 weeks; Mean -12.53 (95%CI -7.76 to -18.3) (p-value <0.0001); Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Significant improvement in Parents Global Assessment at 5 weeks; Group 1: 57/86, Group 2: 20/86; Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 5 weeks; Group 1: 1/86, Group 2: 1/86; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months;

Study	Biederman 2008⁸⁹
study	Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Biederman 2010⁹¹
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=223)
Countries and setting	Conducted in USA; Setting: Massachusetts General Hospital, USA
Line of therapy	Unclear
Duration of study	Intervention time: Just phase I (double blind): 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Unclear
Inclusion criteria	Childhood onset and persistent symptoms, AISRS score of 24 or higher. Anxiety disorder/depression included if on a stable dose of medication. CGI-S score of 3 or lower also included
Exclusion criteria	Other chronic medical conditions, abnormal baseline laboratory values, IQ of less than 80, delirium, dementia, amnesic disorders, other clinically unstable psychiatric conditions, drug or alcohol abuse or dependence within 6 months preceding the study, and previous adequate trial of MPH.
Recruitment/selection of patients	patients fulfilling inclusion criteria at the outpatients clinic at Massachusetts General Hospital, USA
Age, gender and ethnicity	Age - Range: 19 to 60 years. Gender (M:F): 98:125. Ethnicity: not stated
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not stated). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	(n=112) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . OROS methylphenidate. Maximum daily dose of 1.3mg/kg, with an initial dose of 36mg. Mean daily dose 78.4+/- 31.7mg. Duration 6 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:

Study	Biederman 2010 ⁹¹
	(n=115) Intervention 2: No treatment - Placebo. Mean daily dose 96.6+/-26.5mg. Duration 6 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Ortho-McNeil Janssen Scientific Affairs, LLC (and principal author funding from Eli Lilly and others))
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Treatment response at 6 week; Group 1: 67/109, Group 2: 41/114; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at 6 week; Group 1: 12/112, Group 2: 3/115; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Low risk of bias

Study (subsidiary papers)	Biederman 2012 ⁸⁴ (Biederman 2012 ⁸⁵)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline	Adequate method of assessment/diagnosis: A psychiatric evaluation and Structured Clinical Interview for

Study (subsidiary papers)	Biederman 2012 ⁸⁴ (Biederman 2012 ⁸⁵)
condition	DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female outpatients who met full DSM-IV criteria for ADHD, subjects had an onset of symptoms in childhood, a persistence of impairing symptoms into adulthood, and did not have pharmacological treatment within the past month
Exclusion criteria	Any other clinically significant psychiatric or medical conditions, including clinically significant laboratory to ECG values, hypertension, pre-existing structural cardiac abnormalities, or a known hypersensitivity to LDX or any amphetamine compounds. Individuals who used psychotropics or any medication in the past month with clinically significant central nervous system effects, an IQ <80, or a history of substance dependence or abuse within six months preceding the study, pregnant or nursing females and people who had never held a driving license.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 18-26. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Medication was titrated from an initial dose of 30mg at week one to 50mg at week two and to a maximum of 70mg by week three. Subjects experiencing adverse events were able to decrease in increments of 20mg, if determined necessary by the treating clinician. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (n=34) Intervention 2: No treatment - Placebo. No details given. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Funded by Shire Pharmaceuticals Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus PLACEBO	

Study (subsidiary papers)	Biederman 2012 ⁸⁴ (Biederman 2012 ⁸⁵)
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: ADHD-RS at 6 weeks; Group 1: mean -18.4 (SD 12.6); n=31, Group 2: mean -5.4 (SD 9.9); n=30; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Global Assessment of Functioning at 6 weeks; Group 1: mean 63.5 (SD 4.4); n=31, Group 2: mean 58.9 (SD 4.8); n=30; Global Assessment of Functioning 0-100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at 6 weeks; Group 1: 1/35, Group 2: 1/34; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Low risk of bias

Study	Block 2009 ¹⁰⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=288)
Countries and setting	Conducted in USA; Setting: 14 outpatient sites in USA
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	6 to 12 years, met DSM4 criteria for ADHD, scores at least 1.5 SD above age and gender norms on the ADHD RS (Attention deficit /hyperactive disorder rating scale)--parent version
Exclusion criteria	Depression/anxiety, drugs/alcohol abuse within previous three months, psychoactive medication, weight <20 kg or >65 kg at visit 1, uncontrolled hypertension, previous unresponsiveness/intolerability to atomoxetine.

Study	Block 2009 ¹⁰⁰
Recruitment/selection of patients	Recruited during routine office visits for ADHD, by referral, and by advertisement.
Age, gender and ethnicity	Age - Range: 6-12 years. Gender (M:F): 210:78. Ethnicity: 68.8% Caucasian
Further population details	1. ADHD subtype: All/mixed subtypes (Combined 75%). 2. Age: Children (6-12 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Mixed (32% oppositional defiant disorder). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Extra comments	75% of the population met the criteria for combined subtype ADHD(both inattentive and hyperactive/impulsive symptoms). Most common co-morbidity was oppositional defiant disorder
Indirectness of population	No indirectness
Interventions	<p>(n=102) Intervention 1: CNS stimulants - Atomoxetine. Patients in the atomoxetine treatment arms began treatment with a single daily dose of 0.8 mg/kg/day for 3 days with the dose increasing to 1.2 mg/kg/day for the remainder of the first week. Treated patients remained on the atomoxetine 1.2 mg/kg/day throughout the study unless tolerability problems precluded them from continuing on this dose. In this case, the dose was decreased to 0.8 mg/kg/day. Patients with a CGI-ADHD-S score >3 and who had no safety or tolerability contraindications could have their dose increased to 1.2 mg/kg/day. The maximum dose was 1.4 mg/kg/day and could not exceed 10mg/day regardless of weight. Mean final dose 1.25 mg/kg/day taken in AM. Duration 6 weeks. Concurrent medication/care: All patients underwent a minimum 5 day medication free evaluation period. Previous stimulant treatment 28.4%</p> <p>Further details: 1. Dose: 2. Method of titration: Comments: Atomoxetine taken in AM - placebo taken in PM</p> <p>(n=93) Intervention 2: CNS stimulants - Atomoxetine. Patients in the atomoxetine treatment arms began treatment with a single daily dose of 0.8 mg/kg/day for 3 days with the dose increasing to 1.2 mg/kg/day for the remainder of the first week. Treated patients remained on the atomoxetine 1.2 mg/kg/day throughout the study unless tolerability problems precluded them from continuing on this dose. In this case, the dose was decreased to 0.8 mg/kg/day. Patients with a CGI-ADHD-S score >3 and who had no safety or tolerability contraindications could have their dose increased to 1.2 mg/kg/day. The maximum dose was 1.4 mg/kg/day and could not exceed 10mg/day regardless of weight. Mean final dose 1.26 mg/kg/day taken in PM. Duration 6 weeks. Concurrent medication/care: Previous stimulant treatment 30.4%</p> <p>Further details: 1. Dose: 2. Method of titration: Comments: Placebo taken in AM - Atomoxetine taken in PM</p> <p>(n=93) Intervention 3: No treatment - Placebo. Patients received drug twice daily: once in the morning (AM) and once in the evening (PM) just prior to bedtime. Placebo taken AM and PM . Duration 6 weeks. Concurrent medication/care: Previous stimulant treatment 36.6%</p>

Study	Block 2009¹⁰⁰
	Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Lilly USA, LLC)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE GROUPS COMBINED versus PLACEBO AM AND PM GROUP</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome: ADHD RS Total Score at 6 weeks; Risk of bias: All domain – Very High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32, Reason: Adverse event, lack of efficacy, lost to follow up, personal conflict, protocol violation, physician decision, entry criteria not met, protocol criteria not met, noncompliance.; Group 2 Number missing: 27, Reason: Adverse event, lack of efficacy, lost to follow up, personal conflict, protocol violation, physician decision, entry criteria not met, protocol criteria not met, noncompliance.</p>	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Bouffard 2003¹¹⁰
Study type	RCT (Patient randomised; Crossover: 5 days)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Canada; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Telephone screen, Self-report questionnaires, clinic visits and psychiatric evaluation
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	1. DSM-IV criteria for ADHD 2. 1.5 or more on at least 1 ADHD self-report questionnaire (either Conners'

Study	Bouffard 2003 ¹¹⁰
	Adult ADHD Rating Scale or the Adult ADHD Problem Behaviours scale 3. Estimated IQ of 80 or above on abbreviated WAIS-R 4. No psychiatric conditions that better accounted for their current symptoms or required other treatment 5. No substance abuse in the preceding 6 months 6. No medical condition contraindicating stimulants (that is, hypertension or cardiac disease)
Exclusion criteria	Not reported
Recruitment/selection of patients	Referred by physicians, other professionals, family members and by themselves
Age, gender and ethnicity	Age - Range: 17-51. Gender (M:F): 24:6. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=38) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Each drug was given for 4 weeks; each dose was given for 2 weeks. Methylphenidate was started with a 3-day lead in of increasing dosages, as follows: day 1, 5mg 3 times daily; day 2, 10 mg 3 times daily; day 3, 15 mg 3 times daily. If no prohibitive side effects were found, subjects resumed the lower dosage (10mg 3 times daily) and after two weeks the dose was increased to 15 mg 3 times daily for 2 subsequent weeks. Duration 4 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=38) Intervention 2: No treatment - Placebo. Placebo was given in a similar fashion to methylphenidate. Duration 4 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (FRSQ grant for the study of adults with ADHD)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: CAARS at 4 weeks; Group 1: mean 1 (SD 0.6); n=30, Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Behavioural outcomes at <3- or >6-months

- Actual outcome for Adult: Adult ADHD Problem Behaviours Scale at 4 weeks; Group 1: mean 1.2 (SD 0.5); n=30, Risk of bias: High; Indirectness of

Study	Bouffard 2003 ¹¹⁰
outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of bias

Study	Bron 2014 ¹¹⁷
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=27)
Countries and setting	Conducted in Netherlands; Setting: PsyQ outpatient Adult ADHD clinic in The Hague, Netherlands
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DIVA 2.0 (DSM-IV translation?)
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	All participants had taken part in an open label dose optimization trial (Newcorn, 2010). It is unclear how participants were selected from this. Diagnosis of ADHD by a trained psychologist using the Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0). ADHD diagnosis were based on having at least 6 of 9 DSM-IV symptoms of inattention and hyperactivity/impulsivity in childhood, a chronic persisting course of symptoms and impairment, and having at least 4 of 9 DSM-IV symptoms of inattention and hyperactivity/impulsivity in adulthood.
Exclusion criteria	Severe co-morbid psychiatric disorders at the time of screening interview, treatment with stimulants, antipsychotics, clonidine, benzodiazepines or beta-blockers within one month prior to study participation or any medication that could influence the CPT performance (i.e TCA or SSRI), any cognitive disorder like dementia or amnesic disorder, mental retardation
Recruitment/selection of patients	Drug-naive patients with combined subtype of ADHD, from the PsyQ outpatient Adult ADHD clinic in the Hague.
Age, gender and ethnicity	Age - Mean (SD): 30.5 (7.4). Gender (M:F): 17/5. Ethnicity: not reported

Study	Bron 2014 ¹¹⁷
Further population details	1. ADHD subtype: Combined (100% of the study population were of the combined subtype of ADHD). 2. Age: Adults 18-65 years) (Age 18-55 years). 3. At risk population: General population 4. Comorbidities: Mixed (50% mood disorder, 13.6% anxiety disorder, 40.7% substance abuse disorder, 4.5% eating disorder). 5. Diagnostic method: DSM (Diagnoses were based on having at least 6 of 9 DSM-IV symptoms of inattention and hyperactivity/impulsivity in childhood, a chronic persisting course of symptoms and impairment, and having at least 4 of 9 DSM-IV symptoms of inattention and hyperactivity/impulsivity in adulthood). 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Extra comments	100% of the study population were of the combined subtype of ADHD. 77% of the stud population suffered from psychiatry history, of which 50% was mood disorder, 13.6% was anxiety disorder, 40.7% substance use disorder and 4.5% eating disorder.
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). OROS MPH treatment was initiated with a once daily dose of 36 mg and continued with an increment of 36 mg after 7 days, resulting in a total once daily dose of 72 mg for all patients in weeks 3 and 6. All subjects took the drug at 8am ahead of CPT task at 9:30 am. Duration 6 weeks. Concurrent medication/care: not reported Further details: 1. Dose: 2. Method of titration: Fixed dose (n=25) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 6 weeks. Concurrent medication/care: not reported Further details: 1. Dose: 2. Method of titration: Fixed dose
Funding	Academic or government funding (Parnassia Bavo Academy Stimulation Fund , The Hague, Netherlands)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH versus PLACEBO	
Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at 2 weeks; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of bias due to pre-randomisation administration of an intervention to select patients

Study	Brown 2006 ¹¹⁸ ; Weiss 2005 ⁶⁶²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=153)
Countries and setting	Conducted in USA; Setting: Not stated
Line of therapy	Unclear
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) at least average intelligence assessed by WASI (2) anxiety or depressive disorders were not exclusion criteria
Exclusion criteria	(1) Weight less than 25kg (2) documented history of bipolar type I or II (3) history of psychosis (4) intellectual disability (5) any organic brain disease or a history of any seizure disorder (6) taking any psychotropic medication (7) history of alcohol or drug abuse (8) any other significant medical conditions
Recruitment/selection of patients	Recruited through primary care clinicians, mental health professionals and by advertisement
Age, gender and ethnicity	Age - Range: 8 to 12 years. Gender (M:F): 80.4% male. Ethnicity: 60% White, 25% Hispanic, 9% African American, 6% Other
Further population details	1. ADHD subtype: All/mixed subtypes (72.5 combined type). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (33.3% ODD, 29.8% learning disorder). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (59.5% had previous stimulant use). 7. Severity:
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: CNS stimulants - Atomoxetine. Administered once a day in the morning with breakfast. 0.8mg/kg per day for the first 3 days titrated to 1.8mg/kg per day maximum depending on response. Duration 7 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose (n=52) Intervention 2: No treatment - Placebo. Placebo. Duration 7 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly)

Study	Brown 2006 ¹¹⁸ ; Weiss 2005 ⁶⁶²
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
<p>Protocol outcome 1: Quality of life at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): Child Health Questionnaire at 7 weeks; Group 1: mean 7.1 (SD 12.6); n=92, Group 2: mean 3.7 (SD 9.4); n=49; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS (teacher assessed) at 7 weeks; Group 1: mean -10.3 (SD 8.7); n=99, Group 2: mean -5 (SD 6.6); n=51; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): Conners CPRS (parent assessed) at 7 weeks; Group 1: mean -12.1 (SD 12.7); n=99, Group 2: mean -4.1 (SD 7.6); n=51; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: high risk of attrition bias

Study	Buitelaar 2001 ¹²⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Netherlands; Setting: Beele hospital and Groot Emaus hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Psychiatric, psychological and medical examination, and diagnostic and laboratory assessment was completed with information on prior treatment and developmental history
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects were included if 1) their overt aggressive behaviour persisted during hospitalisation, as reflected in a score of at least 1 on the modified Overt Aggression scale rated by nurses in the ward at the end of the

Study	Buitelaar 2001 ¹²⁹
	baseline phase; 2) their aggressive behaviour failed to respond to behavioural treatment approaches (typically these behavioural treatments involve contingency management and social skills training delivered on an individual basis for at least 2 months); 3) there was a clinical indication for drug treatment; 4) they were between 12 and 18 years old; 5) they had a principle diagnosis of conduct disorder, oppositional defiant disorder, or attention-deficit/hyperactivity disorder according to DSM-IV; and 6) they had a full scale IQ between 60 and 90 on the Wechsler Intelligence Scale for Children-Revised
Exclusion criteria	1)Suffering from neurologic, cardiac, pulmonary or hepatic diseases; 2) they were suffering from primary mood disorders, schizophrenia or other active psychosis, or suicidality; 3) they had a comorbid substance abuse disorder according to DSM-IV; 4) if female, they were pregnant or used inadequate contraception; 5) a major change in treatment strategy (such as transition to another ward) was expected in the near future; or 6) it was not considered feasible to discontinue current psychotropic medication
Recruitment/selection of patients	Patients hospitalised in the Beele or Groot Emaus
Age, gender and ethnicity	Age - Mean (SD): Risperidone: 14 (1.5) Placebo: 13.7 (2). Gender (M:F): 33:5. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Young people (13-18 years) 3. At risk population: Secure estate 4. Comorbidities: Mixed (Conduct disorder (30), ODD (6), Disruptive disorder (2)). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: 70% stimulant naive
Interventions	(n=19) Intervention 1: Antipsychotics - Risperidone. Titration began with 0.5mg twice daily at 8am and 9pm. The daily dose could be increased by 1mg daily to a maximum of 5mg twice daily. There was a two week dose-rising phase and a 4 week fixed dose phase. Duration 6 weeks. Concurrent medication/care: All patients were required to discontinue current medication Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Mixed (There was a two week dose-rising phase and a 4 week fixed dose phase). (n=19) Intervention 2: No treatment - Placebo. Patients were given placebo tablets identical to the risperidone tablets. Duration 6 weeks. Concurrent medication/care: All patients were required to discontinue current medication Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Funded by Janssen-Cilag)

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

Study	Buitelaar 2001 ¹²⁹
<p>Protocol outcome 1: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): ABC - Hyperactive subscale at 6 weeks; Group 1: mean 15.8 (SD 8.6); n=19, Group 2: mean 19 (SD 7.5); n=19; Aberrant Behaviour Checklist 0-20 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Serious adverse events at All - Actual outcome for Children (up to 18 years): Serious adverse events at 6 weeks; Group 1: 2/19, Group 2: 1/19; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study (subsidiary papers)	LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013 ¹⁴⁰ (Kooij 2013 ³⁸⁶)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=279)
Countries and setting	Conducted in Belgium, Germany, Netherlands, Spain, Sweden, USA; Setting: 42 European sites
Line of therapy	Unclear
Duration of study	Intervention + follow up: 13 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects were adults (18-65 years) with ADHD according to DSM-IV confirmed using Conners Adult ADHD Diagnostic Interview Part II for DSM-IV. Patients had to score >24 on the 18 DSM-IV items measured by CAARS-O:SV. ADHD was not diagnosed if the symptoms were better accounted for by another psychiatric disorder.
Exclusion criteria	non response to MPH; any clinically unstable psychiatric condition, family history of schizophrenia or affective psychosis, autism, eating disorder, motor tics of Tourette's syndrome, substance use disorder, hyperthyroidism, history of seizures and glaucoma. Pregnant and breastfeeding women were also excluded.

Study (subsidiary papers)	LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013¹⁴⁰ (Kooij 2013³⁸⁶)
Recruitment/selection of patients	42 European sites between February 2008 and April 2009
Age, gender and ethnicity	Age - Range: 18-65 years. Gender (M:F): 146:133. Ethnicity: Predominantly white (~95%), 1% black, 1% Asian and 3% other
Further population details	1. ADHD subtype: All/mixed subtypes (Predominantly combined ADHD subtype (~70%) , predominantly inattentive (~26%) and predominantly hyperactive-impulsive (~3%) and not specified (~0.5%)). 2. Age: Adults 18-65 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Extra comments	Predominantly combined ADHD subtype (~70%), predominantly inattentive (~26%) and predominantly hyperactive-impulsive (~3%) and not specified (~0.5%)
Indirectness of population	No indirectness
Interventions	<p>(n=90) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). After up to 2 weeks screening to enable safe tapering and discontinuations of disallowed medications (4 weeks for monoamine oxidase). Subjects assigned to OROS MPH started at 36 mg. From day 8, these subjects received their randomly assigned dose for 12 weeks. Duration 13 weeks. Concurrent medication/care: concomitant medications to be discontinued during the screening period were adrenergic receptor agonists, antipsychotics, theophylline, coumarin anticoagulants or anticonvulsants, any ADHD treatment , monoamine oxidase inhibitors, herbal and OTC stimulant diet preparations or drugs containing stimulants Further details: 1. Dose: 2. Method of titration:</p> <p>(n=92) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). After up to 2 weeks screening to enable safe tapering and discontinuations of disallowed medications (4 weeks for monoamine oxidase). Subjects assigned to OROS MPH started at 36 mg. From day 8, these subjects received their randomly assigned dose for 12 weeks. Duration 13 weeks. Concurrent medication/care: concomitant medications to be discontinued during the screening period were adrenergic receptor agonists, antipsychotics, theophylline, coumarin anticoagulants or anticonvulsants, any ADHD treatment , monoamine oxidase inhibitors, herbal and OTC stimulant diet preparations or drugs containing stimulants Further details: 1. Dose: 2. Method of titration:</p> <p>(n=97) Intervention 3: No treatment - Placebo. After up to 2 weeks screening to enable safe tapering and discontinuations of disallowed medications (4 weeks for monoamine oxidase). Subjects assigned to placebo received placebo for 13 weeks. Duration 13 weeks. Concurrent medication/care: concomitant medications to be discontinued during the screening period were adrenergic receptor agonists, antipsychotics, theophylline, coumarin anticoagulants or anticonvulsants, any ADHD treatment , monoamine oxidase inhibitors, herbal and OTC stimulant diet preparations or drugs containing stimulants</p>

Study (subsidiary papers)	LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013¹⁴⁰ (Kooij 2013³⁸⁶)
	Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Authors received grants from JanssenOCilag, Medice and Shire)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH 54 MG GROUP versus OROS MPH 72 MG GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnett's procedure except CGI-S at 13 weeks; Group 1: mean 23 (SD 11.1); n=90, Group 2: mean 21.6 (SD 10.2); n=92

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 35, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 29, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Self-Report-Short Version(CAARS-S:SS)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnett's procedure except CGI-S at 13 weeks; Group 1: mean 35.6 (SD 16); n=55, Group 2: mean 35.3 (SD 14.7); n=55

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Self-Report-Short Version including ADHD Index (12 CAARS-S:S)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnett's procedure except CGI-S at 13 weeks; Group 1: mean 16.2 (SD 7.5); n=55,

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: CGI-S (Median-range) at 13 weeks; Placebo= 4.0 (1-6), OROS MPH 54 mg= 4.0 (1-7) and OROS MPH 72 mg = 3.0 (1-7);

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Hamilton Rating Scale for Anxiety (HAM-A) at 13 weeks; Group 1: mean 1.1 (SD 4.7); n=89, Group 2: mean 0.2 (SD 5.4); n=92

Study (subsidiary papers)

LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013¹⁴⁰ (Kooij 2013³⁸⁶)

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Hamilton Rating Scale for Depression (HAM-D17) at 13 weeks; Group 1: mean 0.2 (SD 3.6); n=90, Group 2: mean 0.2 (SD 5.7); n=92; Hamilton Rating Scale for Depression (HAM-D17) 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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 15/89, Group 2: 19/92

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH 54 MG GROUP versus PLACEBO GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnetts procedure except CGI-S at 13 weeks; Group 1: mean 23 (SD 11.1); n=90, Group 2: mean 26.1 (SD 10.6); n=97

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Self-Report-Short Version(CAARS-S:SS)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnetts procedure except CGI-S at 13 weeks; Group 1: mean 35.6 (SD 16); n=90, Group 2: mean 35.3 (SD 14.7); n=92; CAARS-S:S -54 or 0-84 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: groups were matched for age, sex, race, BMI, height,

Study (subsidiary papers)

LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013¹⁴⁰ (Kooij 2013³⁸⁶)

ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Self-Report-Short Version including ADHD Index (12 CAARS-S:S)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnett procedure except CGI-S at 13 weeks; Group 1: mean 16.2 (SD 7.5); n=90, Group 2: mean 18.2 (SD 6.7); n=97

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV); LS mean adjusted; hyperactivity/impulsivity subscale at 13 weeks;

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 35, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 29, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV); LS mean adjusted; inattention subscale at 13 weeks;

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 35, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 29, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 15/89, Group 2: 1/97

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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH 72 MG GROUP versus PLACEBO GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: Investigator rated Conners Adult ADHD Rating Scale-difference in least square mean by ANCOVA, comparing each dose with placebo ,

Study (subsidiary papers)

LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013¹⁴⁰ (Kooij 2013³⁸⁶)

adjusted for multiplicity using the Dunnett's procedure except CGI-S at 13 weeks; Group 1: mean 15.8 (SD 6.8); n=92, Group 2: mean 18.2 (SD 6.7); n=97
 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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other
 - Actual outcome: Self-Report-Short Version(CAARS-S:SS)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnett's procedure except CGI-S at 13 weeks; Group 1: mean 35.3 (SD 14.7); n=92, Group 2: mean 35.6 (SD 16); n=97
 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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other
 - Actual outcome: Self-Report-Short Version including ADHD Index (12 CAARS-S:S)-difference in least square mean by ANCOVA, comparing each dose with placebo , adjusted for multiplicity using the Dunnett's procedure except CGI-S at 13 weeks; Group 1: mean 15.8 (SD 6.8); n=92, Group 2: mean 18.2 (SD 6.7); n=97
 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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other
 - - Actual outcome: Serious adverse events (suicide attempt) at 13 weeks;
 Risk of bias: All domain - ; Indirectness of outcome: No indirectness
 - Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV); LS mean adjusted; hyperactivity/impulsivity subscale at 13 weeks;
 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 35, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 29, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other
 - Actual outcome: Investigator rated Conners Adult ADHD Rating Scale (CAARS-O: SV); LS mean adjusted; inattention subscale at 13 weeks;
 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 35, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 29, Reason: discontinuation, adverse events, lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other

Study (subsidiary papers)	LAMDA-II (EudraCT number: 2007-002111-82) trial: Casas 2013 ¹⁴⁰ (Kooij 2013 ³⁸⁶)
Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 19/92, Group 2: 1/97 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: groups were matched for age, sex, race, BMI, height, ADHD subtype, baseline CARRS-O-SV scores; Group 1 Number missing: 55, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other; Group 2 Number missing: 68, Reason: discontinuation, adverse events,lack of efficacy, non-compliance, withdrew consent, lost to follow-up, other	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Casat 1987 ¹⁴² (Casat 1989 ¹⁴¹)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III criteria based on history and clinical observation
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children were either treatment naive or unresponsive to conventional stimulant therapy. Concurrence of parent and teacher scores on the Conners parent and teacher questionnaires (>1.5 on the Hyperactive factor for the teacher, and >1.5 on the Impulsive-Hyperactive or Restless-Immature factors for the parent)
Exclusion criteria	IQ of less than 70 on the WISC-R, history of seizure disorder, tic disorder, any unstable medical condition, and known hypersensitivity to psychotropic medications.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 6.3-12.4. Gender (M:F): 25:5. Ethnicity: White (73%), Black (27%)
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) (6.3-12.4). 3. At risk population: General population 4. Comorbidities: Conduct disorder (1 subject had a secondary diagnosis of

Study (subsidiary papers)	Casat 1987 ¹⁴² (Casat 1989 ¹⁴¹)
	CD). 5. Diagnostic method: DSM (DSM-III criteria based on history and clinical observation). 6. Line of treatment: 1st line (drug naive) (4/30 had previous treatment). 7. Severity: Not applicable / Not stated / Unclear (>1.5 on the Hyperactive factor for the teacher, and >1.5 on the Impulsive-Hyperactive or Restless-Immature factors for the parent).
Indirectness of population	No indirectness
Interventions	<p>(n=20) Intervention 1: Bupropion. The midpoints of three weight ranges (20 to 30 kg, 30 to 40 kg and >40 kg) were used to determine an approximate 3mg/kg dosage on days 1-3, which was gradually escalated to approximately 6mg/kg on Days 15-28. A maximum final dose of 150mg/day was given in the lowest weight range, 200mg/day in the middle weight range and 250mg/day in the heaviest weight range. Medication was given twice a day, at 7am and 7pm. Duration 6 weeks. Concurrent medication/care: All children were free of all medication for 14 days prior to study entry Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=10) Intervention 2: No treatment - Placebo. Placebo was given as identical 50mg and 75mg tablets, matched to bupropion. Duration 6 weeks. Concurrent medication/care: All children were free of all medication for 14 days prior to study entry Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Funded by the Burroughs-Wellcome Company)

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

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Children (up to 18 years): CGI-I at 6 weeks; Group 1: mean 2.89 (SD 0.88); n=18, Group 2: mean 3.44 (SD 0.73); n=10; CGI-I 0-7 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): CPTQ-P at 6 weeks; Group 1: mean 11.26 (SD 4.48); n=18, Group 2: mean 19.44 (SD 6.98); n=10; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): CPTQ-T at 6 weeks; Group 1: mean 14.57 (SD 6.57); n=18, Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 6 weeks; Group 1: 1/20, Group 2: 0/10; Risk of bias: Low; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Casat 1987 ¹⁴² (Casat 1989 ¹⁴¹)
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study	Chronis-Tuscano 2008 ¹⁶²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=23)
Countries and setting	Conducted in USA; Setting: Treatment providers in the Washington DC metropolitan area, including families who had been seen at the University of Maryland ADHD program and the Children's National Medical Centre Hyperactivity & Learning Problems Clinic (Washington DC)
Line of therapy	1st line
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Mothers were included in the study were administered the structured Clinical Interview for DSM-IV (SCID) to assess other psychiatric disorders. Past and current collateral reports of ADHD symptoms from individuals close to the participant.
Exclusion criteria	Mothers were excluded on the basis of any current Axis I disorder other than ADHD, Beck Depression Inventory-II scores consistently above 16 , severe tics or Tourette's syndrome, a history of seizures or abnormal electroencephalogram, high blood pressure, narrowing/blockage of the GI tract, positive urine drug screen at intake or concomitant psychotropic medication use
Recruitment/selection of patients	Mothers and their children were recruited from treatment provider after completing a brief telephone screen during which suitability was assessed using the CAARS-S:SV. T scores on the ADHD index had to fall a minimum of >1.5 standard deviations above the mean for the participant's age and gender to proceed to the diagnostic assessment. Study took place in two phases. Medication was titrated over a period of 5 weeks to each participant's maximally effective dose of OROS methylphenidate. Participants began the titration with a placebo dose and dose was increased weekly from placebo to OROS MPH 36 mg/day, 54 mg/day, 72

Study	Chronis-Tuscano 2008 ¹⁶²
	mg/day up to a maximum dose of 90 mg/ day until the medication was well tolerated and certain criteria were met. if these criteria were achieved at a dose less than 90 mg, the current dose was maintained until the end of phase 1
Age, gender and ethnicity	Age - Mean (SD): 39.78(5.53). Gender (M:F): 100% female. Ethnicity: 91.3% white, 4.3% Asian and 4.3% Hispanic
Further population details	1. ADHD subtype: All/mixed subtypes (56.5% of the study population comprising mothers were of the combined subtype of ADHD, 34.8% of the inattentive subtype and 8.7% of the hyperactive/impulsive subtype). 2. Age: Adults 18-65 years) (mean (SD): 39.78 (5.53)). 3. At risk population: Looked after children 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (Mothers were given SCID, reports were taken from those who lived with or were in close contact with mothers). 6. Line of treatment: 1st line (drug naive) (Mothers were drug-naive). 7. Severity: Not applicable / Not stated / Unclear
Extra comments	Participants included mothers, 56.5% of the study population comprising mothers were of the combined subtype of ADHD, 34.8% of the inattentive subtype and 8.7% of the hyperactive/impulsive subtype. Other comorbid conditions were an exclusion criteria
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . During phase 2, mothers were randomly assigned to their maximally effective dose (based on phase 1 titration) or placebo. 1 participant received 54 mg, 3 received 72 mg and 5 received 90 mg. Duration 2 weeks. Concurrent medication/care: No concomitant psychotropic treatment was allowed during the study Further details: 1. Dose: Mixed (1 received 54mg, 3 received 72mg, 5 received 90mg). 2. Method of titration: Fixed dose (fixed dose during phase 2). (n=11) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 2 weeks. Concurrent medication/care: No concomitant psychotropic treatment was allowed during the study Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Supported by McNeil Pediatrics, Division of McNeil-PPC Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH GROUP versus PLACEBO GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: CAARS Self-report Inattention sub-scale at 2 weeks; Group 1: mean 57.78 (SD 15.75); n=9, Group 2: mean 65.55 (SD 16.31); n=11; CAARS Self-report 0-84 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adult: CAARS Self-report Hyperactivity/impulsivity sub-scale at 2 weeks; Group 1: mean 49.33 (SD 17.06); n=9, Group 2: mean 48.27 (SD 17.32); n=11; CAARS Self-Report 0-84 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Chronis-Tuscano 2008 ¹⁶²
	- Actual outcome for Adult: CAARS Self-report ADHD index sub-scale at 2 weeks; Group 1: mean 54.44 (SD 12.82); n=9, Group 2: mean 60.27 (SD 18.07); n=11; CAARS Self-Report 0-84 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of bias

Study	Coghill 2007 ¹⁷²
Study type	RCT (Patient randomised; Crossover: Not stated)
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in United Kingdom; Setting: Tayside child and adolescent psychiatric service
Line of therapy	2nd line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Drug naive boys with ODD, CD, anxiety disorder, depressive disorder, tic disorder, and social phobia, were included. (2) +1.5 SDs from the mean on Conners' Teacher Rating Scale short version 26 and 28.
Exclusion criteria	(1) Neurological impairment (2) learning disability (3) chronic physical illness (4) sensory or motor impairment (5) current or previous exposure to stimulant medication (6) abuse of illegal drugs
Recruitment/selection of patients	boys recruited from consecutive outpatient referrals (aged 7-15 years) to the Tayside child and adolescent psychiatric service
Age, gender and ethnicity	Age - Range: 7 to 15 years. Gender (M:F): All males. Ethnicity: Not stated
Further population details	1. ADHD subtype: Combined 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM IV and ICD-10 used). 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Extra comments	Combined subtype and comorbid hyperkinetic disorder only

Study	Coghill 2007 ¹⁷²
Indirectness of population	No indirectness
Interventions	<p>(n=25) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). 0.3mg/kg twice daily at 08:00 and midday. Crossover blocks of 4 weeks: MPH administration was continued for three cross-over periods of 28 days after initial assessment at 2 weeks from baseline testing. Participants were tested 90 mins after taking morning medication at the end of each 28 day block. Duration 4 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:</p> <p>(n=25) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). 0.6mg/kg twice daily at 08:00 and midday. Crossover blocks of 4 weeks: MPH administration was continued for three cross-over periods of 28 days after initial assessment at 2 weeks from baseline testing. Participants were tested 90 mins after taking morning medication at the end of each 28 day block. Duration 4 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration:</p> <p>(n=25) Intervention 3: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration:</p>
Funding	Other (Local trust - TENOVUS-Scotland initiative)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE LOW DOSE (0.3 MG/KG/DOSE) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: Parent Conners' Global Index at 4 weeks; Group 1: mean 67.2 (SD 13.5); n=25, Group 2: mean 77.2 (SD 11.1); n=25 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline scale scores or change scores not reported-statement that there were no differences at baseline with respect to age,BPVS percentile rank, parent or teacher rated ADHD composite Conners scores and incidence of co-morbid disorders other than separation anxiety disorder; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Teachers Conners' Global Index at 4 weeks; Group 1: mean 65 (SD 14.1); n=25, Group 2: mean 58.5 (SD 12.8); n=25; Teachers Conners Global Index 0-100? Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline scale scores or change scores not reported-statement that there were no differences at baseline with respect to age,BPVS percentile rank, parent or teacher rated ADHD composite Conners scores and incidence of co-morbid disorders other than separation anxiety disorder; Group 1 Number missing: ; Group 2 Number missing:</p>	

Study	Coghill 2007 ¹⁷²
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE HIGH DOSE 0.6MG/KG/DOSE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: Parent Conners' Global Index at 4 weeks; Group 1: mean 67 (SD 14.8); n=25, Group 2: mean 77.2 (SD 11.1); n=25; CGI 0-100? Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline scale scores or change scores not reported-statement that there were no differences at baseline with respect to age,BPVS percentile rank, parent or teacher rated ADHD composite Conners scores and incidence of co-morbid disorders other than separation anxiety disorder; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Teachers Conners' Global Index at 4 weeks; Group 1: mean 58.5 (SD 12.8); n=25, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline scale scores or change scores not reported-statement that there were no differences at baseline with respect to age,BPVS percentile rank, parent or teacher rated ADHD composite Conners scores and incidence of co-morbid disorders other than separation anxiety disorder; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Clinical Global Impressions-Improvement-CGI-I at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline scale scores or change scores not reported-statement that there were no differences at baseline with respect to age,BPVS percentile rank, parent or teacher rated ADHD composite Conners scores and incidence of co-morbid disorders other than separation anxiety disorder; Group 1 Number missing: ; Group 2 Number missing:</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	NCT00763971 trial: Coghill 2013 ¹⁶⁷ (Coghill 2014 ¹⁷¹ , Banaschewski 2013 ⁶¹ , Coghill 2014 ¹⁷⁰)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=336)
Countries and setting	Conducted in Belgium, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, Sweden; Setting: Multiple European centres
Line of therapy	Unclear

Study (subsidiary papers)	NCT00763971 trial: Coghill 2013¹⁶⁷ (Coghill 2014¹⁷¹, Banaschewski 2013⁶¹, Coghill 2014¹⁷⁰)
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ADHD-RS-IV score of 28 or higher (2) age appropriate intellectual functioning (3) normal blood pressure measurements
Exclusion criteria	(1) pregnancy (2) failure to respond to OROS-MPH (3) comorbid psychiatric condition, other than ODD (4) laboratory abnormalities (5) substance abuse or dependence disorder, excluding nicotine (6) seizures, tics, Tourette's (7) current ADHD treatment that is providing effective control of symptoms (8) failure to respond to a course of methylphenidate, or intolerance to amphetamines or methylphenidate.
Recruitment/selection of patients	study conducted between 17 November 2008 and 16 March 2011 at 48 centres in 10 European countries (Germany, Sweden, Spain, Hungary, France, the UK, Italy, Belgium, Poland and the Netherlands)
Age, gender and ethnicity	Age - Mean (SD): 10.9(2.8) Range=6 -17 years. Gender (M:F): 268:64. Ethnicity: 98% Hispanic, 2% other
Further population details	1. ADHD subtype: All/mixed subtypes (68.7% combined). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Mixed line (including drug naive) (55% previously treated with ADHD medication). 7. Severity:
Extra comments	68.7% combined ADHD subtype
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. 4 week stepwise dose optimization period (visits 1-4) and 3 week dose maintenance period (visits 5-7), followed by 1 week washout (visit 8). Daily dose of 30, 50 or 70mg capsules. Patients initially received 30 mg/day .If an acceptable response was not achieved, dose adjustments were made in a stepwise manner at weekly intervals to higher doses .An acceptable response was defined as at least 30% reduction in ADHD-RS-IV total score from baseline and CGI-I rating of 1 (very much improved) or 2 (much improved) with tolerable adverse effects. A reduction of one dose level was permitted if individuals experienced an intolerable adverse effect. Doses could not be modified after visit 3; patients unable to tolerate the drug were withdrawn from the study. Patients who achieved an acceptable response were maintained on their optimal dose for remainder of study (visits 4-7). Duration 7 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration: (n=111) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). Daily dose of 18, 36 or 54mg4 week stepwise dose optimization period (visits 1-4) and 3 week dose maintenance

Study (subsidiary papers)	NCT00763971 trial: Coghill 2013¹⁶⁷ (Coghill 2014¹⁷¹, Banaschewski 2013⁶¹, Coghill 2014¹⁷⁰)
	<p>period (visits 5-7), followed by 1 week washout (visit 8). Daily dose of 18, 36 or 54mg tablets. Patients initially received 30 mg/day .If an acceptable response was not achieved, dose adjustments were made in a stepwise manner at weekly intervals to higher doses. An acceptable response was defined as at least 30% reduction in ADHD-RS-IV total score from baseline and CGI-I rating of 1 (very much improved) or 2 (much improved) with tolerable adverse effects. A reduction of one dose level was permitted if individuals experienced an intolerable adverse effect .Doses could not be modified after visit 3; patients unable to tolerate the drug were withdrawn from the study. Patients who achieved an acceptable response were maintained on their optimal dose for remainder of study (visits 4-7). Duration 7 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration:</p> <p>(n=110) Intervention 3: No treatment - Placebo. Placebo. Duration 7 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Shire Development LLC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS-IV (Least square mean data-not mention of covariates adjusted for) investigator rated at 7 weeks; Group 1: mean -24.3 (SD 10.73); n=80, Group 2: mean -18.7 (SD 9.46); n=74; ADHD-RS-IV 0-54 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age, sex, race, BMI, ADHD scales at baseline, ADHD subtype, concomitant psychiatric diagnosis and previous ADHD medication; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 38, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other

- Actual outcome: Conners Parent rating scale-revised at 7 weeks; Group 1: mean -24.9 (SD 16.1); n=80, Group 2: mean -19.1 (SD 18.1); n=74; CPRS-R 0-81 Top=High is poor outcome

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age, sex, race, BMI, ADHD sub-type, time since diagnosis, concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 33 , Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 38, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other

- Actual outcome: CGI-I-possible responder criteria given in proportion for all comparisons at 7 weeks; Proportion; , Comments: Proportion (and CI) of

Study (subsidiary papers)	NCT00763971 trial: Coghill 2013 ¹⁶⁷ (Coghill 2014 ¹⁷¹ , Banaschewski 2013 ⁶¹ , Coghill 2014 ¹⁷⁰)
<p>patients with rating of 1 (very much improved) or 2 (much improved) at end point. LDX 78% (70-86). OROS-MPH 61% (51-70) LDX =75/104 OROS-MPH = 57/107 Placebo = 13/106 Number of responders in treatment naive subgroup 47/147 LDX 38/47 MPH 33/58 Placebo 10/55; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 33 , Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 38, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other - Actual outcome: WFIRS-P total change scores (subscales are reported separately but too may outcomes to report) at 7 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age, sex, race, BMI,ADHD scales at baseline, ADHD subtype, concomitant psychiatric diagnosis and previous ADHD medication; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 38, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome: adverse event leading to discontinuation of drug at 7 weeks; Group 1: 5/80, Group 2: 2/72 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 ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 38, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other</p>	<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: ADHD-RS-IV (Least square mean data-not mention of covariates adjusted for) at 7 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores75;13 Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason:</p>

Study (subsidiary papers)

NCT00763971 trial: Coghill 2013¹⁶⁷ (Coghill 2014¹⁷¹, Banaschewski 2013⁶¹, Coghill 2014¹⁷⁰)

AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other

- Actual outcome: Conners Parent rating scale-revised at 7 weeks; Group 1: mean -24.9 (SD 16.1); n=80, Group 2: mean -5 (SD 8.42); n=42; CPRS-R 0-81 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other

- Actual outcome: WFIRS-P total change scores (subscales are reported separately but too many outcomes to report) at 7 weeks;

Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome: adverse event leading to discontinuation of drug at 7 weeks; Group 1: 5/80, Group 2: 4/63

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 ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other

Protocol outcome 3: Academic outcomes (literacy and numeracy) at <3- or >6-months

- Actual outcome: CHIP-CE PRF academic achievement subscale at 7 weeks;

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age, sex, race, BMI, ADHD scales at baseline, ADHD subtype, concomitant psychiatric diagnosis and previous ADHD medication; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 60, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS-IV (Least square mean data-not mention of covariates adjusted for) at 7 weeks; Group 1: mean -18.7 (SD 9.46); n=74, Group 2: mean -5.7 (SD 7.13); n=42

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 38, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason: AEs 4,

Study (subsidiary papers)	NCT00763971 trial: Coghill 2013¹⁶⁷ (Coghill 2014¹⁷¹, Banaschewski 2013⁶¹, Coghill 2014¹⁷⁰)
<p>non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other - Actual outcome: Conners Parent rating scale-revised at 7 weeks; Group 1: mean -19.1 (SD 18.1); n=74, Group 2: mean -5 (SD 8.42); n=42 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 38, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome: adverse event leading to discontinuation of drug at 7 weeks; Group 1: 2/72, Group 2: 4/63 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 ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 38, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other</p> <p>Protocol outcome 3: Academic outcomes (literacy and numeracy) at <3- or >6-months - Actual outcome: CHIP-CE PRF academic achievement subscale at 7 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable for age,sex,race,BMI,ADHD sub-type,time since diagnosis,concomitant psychiatric disorder, previous history of ADHD medication and baseline ADHD scale scores; Group 1 Number missing: 33, Reason: 7 AEs, 6 non compliance, 9 refused further participation, 33 lack of efficacy (22 in MPH), 15 other; Group 2 Number missing: 68, Reason: AEs 4, non compliance 2, 4 refused further participation, 54 lack of efficacy, 4 other</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Emotional dysregulation at <3- or >6-months

Study	Conners 1980¹⁷⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks

Study	Conners 1980 ¹⁷⁸
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician diagnosed hyperkinesis
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Aged between six years and zero months and eleven years and nine months 2) Verbal, performance, or full scale IQ of Wechsler's Intelligence scale for Children (WISC) was 80 or above 3) Physician diagnosed hyperkinesis due to minimal brain dysfunction 4) Visual and auditory acuity was sufficient for normal learning process (i.e. 20/50 acuity in one eye, and no bilateral hearing loss greater than 20 dB 5) Family was stable 6) No obsessive, compulsive or phobic behaviour was exhibited by the child 7) The child had normal laboratory values in relation to the established paediatric norms for the laboratory used 8) There was no current medical illness or medical history that contraindicated prescribed drug therapy 9) All prior therapy for hyperkinesis was discontinued for a minimum of eight days prior to beginning administration of study medication. 10) There was no demonstrable or suspected need for anti-seizure medications 11) No concurrent therapy referable to a chronic illness was being used 12) Current ratings on parent and school report showed moderate to severe symptoms of restlessness, inattentiveness, impulsivity, emotional lability, and distractibility 13) Family physician or paediatrician consented to participation
Exclusion criteria	Patients receiving phenothiazines within the previous six months were not admitted into the study.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 6-11. Gender (M:F): 57:3. Ethnicity: White (59), Black (1)
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: Not applicable / Not stated / Unclear (Physician diagnosed hyperkinesis). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . Mean dose 22 mg/day. Methylphenidate was increased in 5mg steps from an initial dosage of 10 mg/day to a maximum of 60 mg/day. Duration 8 weeks. Concurrent medication/care: No concurrent therapy was permitted in the study Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=21) Intervention 2: No treatment - Placebo. Placebo tablets were given in morning and afternoon bottles identical to the active medication. Duration 8 weeks. Concurrent medication/care: No concurrent therapy was permitted in the study Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not

Study	Conners 1980¹⁷⁸
	stated / Unclear
Funding	Academic or government funding (The study was supported by a grant from the National Institute of Mental Health Psychopharmacology branch)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Conners Parent Questionnaire at 8 weeks; Group 1: mean 0.46 (SD 0.23); n=19, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Teacher Questionnaire at 8 weeks; Group 1: mean 1.28 (SD 0.67); n=19, Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Conners 1996¹⁷⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=109)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: physician diagnosis, based on history and examination
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable

Study	Conners 1996 ¹⁷⁷
Inclusion criteria	1) A score of moderate illness severity on the Child Diagnostic Scale; 2) a physician diagnosis of ADDH, based on history and examination; 3) occurrence of mean parent and teacher scores of at least 1.5 on the Conners Parent Questionnaire Hyperactive-Immature or Conduct Disorder factors, and the Hyperactive or Conduct Disorder factors from the Conners Teacher Questionnaire and 4) in good physical health and without evidence of laboratory, EEG or ECG abnormalities.
Exclusion criteria	1) WISC-R IQ <70; 2) body weight <20kg; 3) girls who had passed menarche; 4) known hypersensitivity to psychotropic medication; and 5) history or presence of seizure or tic disorders.
Recruitment/selection of patients	Subjects were recruited from university based outpatient psychiatry clinics, and at one site subjects were recruited from child psychiatric inpatient admissions. All sites also placed local advertisements
Age, gender and ethnicity	Age - Range: 6-12. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: Not applicable / Not stated / Unclear 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=72) Intervention 1: Bupropion. All treatment-phase medications were administered twice daily at 7am and 7pm. Dosage was escalated from 3mg/kg of body weight from day 1 to day 3 to 6mg/kg from day 15 to day 28. A maximum daily dose of 150mg/day was established for the lowest weight range (20 to 30kg), 200mg/day for the middle range (31 to 40kg), and 250 mg/day for the heaviest range (>40 kg). Duration 4 weeks. Concurrent medication/care: All subjects had to be free of psychotropic medication for a minimum of 14 days prior to study entry Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=37) Intervention 2: No treatment - Placebo. Subjects were given matching placebo tablets. Duration 4 weeks. Concurrent medication/care: All subjects had to be free of psychotropic medication for a minimum of 14 days prior to study entry Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Partially supported by Career Science Award from the NIMH to Dr Conners)

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

Study	Conners 1996 ¹⁷⁷
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Conners Abbreviated Parent Questionnaire at 4 weeks; Group 1: mean 13.81 (SD 6.83); n=62, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Abbreviated Teacher Questionnaire at 4 weeks; Group 1: mean 14.67 (SD 6.97); n=54, Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 4 weeks; Group 1: 4/72, Group 2: 0/37; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Low risk of bias

Study	Connor 2010 ¹⁸¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=217)
Countries and setting	Conducted in USA; Setting: 33 sites in the United States
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV diagnosis of ADHD based on a detained psychiatric evaluation using the Kiddie Schedule for Affective Disorders and Schizophrenia
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	A baseline score of 24 or more on the ADHD-RS-IV and a baseline score of 14 or more for males and 12 or more for females on the oppositional subscale of CPRS-R:L
Exclusion criteria	Any current co-morbid psychiatric diagnosis (except ODD, dysthymia or simple phobias), weight <55 lb (<25 kg), pre-existing cardiovascular complications, or current use of medications that affect the CNS, blood pressure or heart rate (except for ADH therapies, which were discontinued during the washout period)

Study	Connor 2010 ¹⁸¹
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 6-12. Gender (M:F): Male 68.7%, Female 31.3%. Ethnicity: White (66.4%), Black or African-American (22.4%), Hawaiian or other Pacific Islander (0.5%), American Indian or Alaska Native (2.8%), Other (7.9%)
Further population details	1. ADHD subtype: All/mixed subtypes (Inattentive (12.6%), Hyperactive (3.3%), Combined (84.1%)). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear (Baseline scores of 24 or more on the ADHD-RS-IV and 14 or more for males and 12 or more for females on the CPRS-R:L).
Indirectness of population	No indirectness
Interventions	<p>(n=138) Intervention 1: Guanfacine. Guanfacine modified release, the dose was increased in 1mg/week increments (to a maximum of 4mg/day) based on tolerance. Following this, subjects' doses were maintained at their optimal level for 3 weeks although a dose reduction of 1mg/day was allowed, if necessary, for tolerability reasons. Duration 8 weeks. Concurrent medication/care: After screening, subjects underwent a washout period that ranged from 3 days to 5 weeks during which all ADHD and other psychoactive medications were discontinued. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=79) Intervention 2: No treatment - Placebo. Subjects had a matching dose optimisation period for five weeks. Duration 8 weeks. Concurrent medication/care: After screening, subjects underwent a washout period that ranged from 3 days to 5 weeks during which all ADHD and other psychoactive medications were discontinued. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Funded by Shire Development Inc)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS at 8 weeks; Group 1: mean -23.8 (SD 9.90125); n=109, Group 2: mean -11.5 (SD 9.90125); n=48; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinued due to adverse events at 8 weeks; Group 1: 14/138, Group 2: 1/79; Risk of bias: Low;

Study	Connor 2010 ¹⁸¹
Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: Very high due to attrition and outcome reporting Protocol outcome 2: Low

Study	Davari-Ashtiani 2010 ¹⁹⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=34)
Countries and setting	Conducted in Iran; Setting: Child and adolescent psychiatric outpatient clinic of Imam-Hosseini Hospital (Tehran, Iran)
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	Met DSM-IV-TR diagnostic criteria for ADHD
Exclusion criteria	(1) Evidence of an intellectual disability or a major psychiatric problem other than oppositional defiant disorder or conduct disorder (2) medical conditions that would preclude the safe use of methylphenidate or bupropion.
Age, gender and ethnicity	Age - Range: 6-12 years. Gender (M:F): 67% male, 33% female. Ethnicity: not specified
Further population details	1. ADHD subtype: Combined (All children diagnosed with combined subtype). 2. Age: Children (6-12 years) (Children aged 6-12 years (mean age = 8.5 years)). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Not applicable / Not stated / Unclear (Not stated. Most comorbidities excluded with the exception of ODD or CD (proportion of participants with ODD or CD not reported)). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: 1st line (drug naive) (All children newly diagnosed and had never received treatment for ADHD). 7. Severity: Not applicable / Not stated / Unclear (Medication titrated to optimal effect, up to 60mg/day for methylphenidate and 45mg/day for bupropion).

Study	Davari-Ashtiani 2010 ¹⁹⁸
Indirectness of population	No indirectness
Interventions	<p>(n=16) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Dose initiated at 0.5 mg/kg/day, and then adjusted to the optimal dosage based on the regular reports provided by the teachers and parents. The maximum dose was 60 mg/day. Duration 6 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: Not applicable / Not stated / Unclear (Not specified. Maximum dose = 60 mg/day). 2. Method of titration: Titrated to optimum dose (Titrated to optimum dose).</p> <p>(n=18) Intervention 2: No treatment - Standard treatment. Dose initiated at 0.5 mg/kg/day, and then adjusted to the optimal dosage based on the regular reports provided by the teachers and parents. The maximum dose was 45 mg/day. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear (Not specified. Maximum dose = 45 mg/day). 2. Method of titration: Titrated to optimum dose (Titrated to optimum dose).</p>
Funding	Academic or government funding (Behavioural Sciences Research Center of Shahid Beheshti University of Medical Sciences (Tehran, Iran))
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUSPIRONE versus METHYLPHENIDATE</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): \geq30% reduction in scores on the ADHD-RS (parent rated) at 6 weeks; Group 1: 14/18, Group 2: 14/16; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Serious adverse events at All - Actual outcome for Children (up to 18 years): Serious adverse events (no description) at 6 weeks; Group 1: 0/18, Group 2: 0/16; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to side effects at 6 weeks; Group 1: 1/18, Group 2: 0/16; Risk of bias: high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1 (ADHD symptoms): high risk of attrition bias

Study	Davari-Ashtiani 2010¹⁹⁸
	Protocol outcome 2 (serious adverse events): very high risk of bias due to (1) high risk of attrition bias, and (2) high risk of measurement bias (outcome not adequately defined) Protocol outcome 3 (drop out due to adverse events): low risk of bias

Study	De Jong 2009²⁰⁰
Study type	RCT (Patient randomised; Crossover: 2 week washout)
Number of studies (number of participants)	(n=36)
Countries and setting	Conducted in Belgium, Netherlands; Setting: Outpatient clinics in the Netherlands and Belgium
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks (each arm)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical diagnosis of ADHD if DBD scores fell at least in the subclinical range (above the 90th percentile) and ADHD- combined type criteria were met on the PDISC-IV
Exclusion criteria	(1) obsessive compulsive disorder, tic disorder, depression, or conduct disorder (2) raw score of 40 or higher on the CDRS scale (3) prior or current diagnosis of pervasive developmental disorder, anxiety disorder, post-traumatic stress disorder, and neurological disorders such as epilepsy, as assessed by clinicians (4) severe arithmetic deficits excluded (defined by a delay greater than 20 school months on the Speeded Arithmetic Test, and a score below the 3rd percentile on the Cognitive Subscales for Arithmetic. (5) IQ below 80 excluded (on WISC-III).
Recruitment/selection of patients	April 2005 to December 2007
Age, gender and ethnicity	Age - Range: 8 to 12 years. Gender (M:F): 29:17. Ethnicity: Not specified
Further population details	1. ADHD subtype: Combined 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear line. 11 in the ADHD group and 4 in the ADHD + reading disorder group had previously received methylphenidate). 7. Severity: Not applicable / Not stated / Unclear
Extra comments	Combined ADHD type only. ADHD condition and ADHD and reading disorder condition.
Indirectness of population	No indirectness

Study	De Jong 2009 ²⁰⁰
Interventions	<p>(n=20) Intervention 1: CNS stimulants - Atomoxetine. Dose was based on a child's weight and was initiated at approximately 0.6mg/kg per day for the first 7 days. The dose for the next 21 days was 1.2mg/kg per day. Mean dose (SD) = 1.11 (0.12) mg/kg per day. Administered once daily in the morning or twice daily when children were unable to tolerate a single dose. Unused pills were returned to assess compliance. If more than 2 consecutive days of full doses of medication or failing to take at least 80% of medication, patients were excluded. 2 week washout between conditions. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:</p> <p>(n=20) Intervention 2: No treatment - Placebo. Duration 4 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:</p> <p>(n=16) Intervention 3: CNS stimulants - Atomoxetine. Dose was based on a child's weight and was initiated at approximately 0.6mg/kg per day for the first 7 days. The dose for the next 21 days was 1.2mg/kg per day. Mean dose (SD) = 1.11 (0.12) mg/kg per day. Administered once daily in the morning or twice daily when children were unable to tolerate a single dose. Unused pills were returned to assess compliance. If more than 2 consecutive days of full doses of medication or failing to take at least 80% of medication, patients were excluded. 2 week washout between conditions. Duration 4 weeks. Concurrent medication/care: not specified Further details: 1. Dose: 2. Method of titration:</p> <p>(n=16) Intervention 4: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: not specified Further details: 1. Dose: 2. Method of titration:</p>
Funding	Principal author funded by industry (Eli Lilly and Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (ADHD AND READING DISORDER) versus PLACEBO (ADHD AND READING DISORDER)

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): CGI-S (final values) adjusted for baseline at 4 weeks; Group 1: mean 3.65 (SD 0.94); n=20, Group 2: mean 4.34 (SD 0.89); n=20; CGI-S 1-7 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-IV Total score (final values) adjusted for baseline at 4 weeks; Group 1: mean 22.44 (SD 10.64); n=20, Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-IV inattention subscale (final values) at 4 weeks; Group 1: mean 12.25 (SD 5.46); n=20, Group

Study	De Jong 2009 ²⁰⁰
	<p>2: mean 18.28 (SD 4.87); n=20; ADHD RS IV SUBSCALE 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: --</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity-impulsivity subscale (final values) at 4 weeks; Group 1: mean 10.32 (SD 5.68); n=20, Group 2: mean 17.03 (SD 5.01); n=20; ADHD-RS-IV SUBSCALE 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: --</p> <p>- Actual outcome for Children (up to 18 years): CGI-I (final values) adjusted for baseline at 4 weeks; Group 1: mean 2.98 (SD 1.07); n=20, Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (ADHD ONLY) versus PLACEBO (ADHD ONLY)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV Total score (final values) adjusted for baseline at 4 weeks; Group 1: mean 30.86 (SD 8.56); n=16, Group 2: mean 35.2 (SD 7.12); n=16; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV inattention subscale (final values) adjusted for baseline at 4 weeks; Group 1: mean 15.27 (SD 4.36); n=16, Group 2: mean 17.82 (SD 3.72); n=16; ADHD RS IV subscale 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity-impulsivity subscale (final values) adjusted for baseline at 4 weeks; Group 1: mean 15.51 (SD 4.56); n=16, Group 2: mean 17.24 (SD 3.84); n=16; ADHD RS IV SUBSCALE 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): CGI-I (final values) adjusted for baseline at 4 weeks; Group 1: mean 3.69 (SD 0.96); n=16, Group 2: mean 3.7 (SD 0.92); n=16; CGI-I 1-7 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): CGI-S (final values) adjusted for baseline at 4 weeks; Group 1: mean 4.05 (SD 0.84); n=16, Group 2: mean 3.73 (SD 0.76); n=16; CGI-S 1-7 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Very high risk of bias due to (1) estimated attrition bias (2) high rate of attrition bias

Study	Dell'agnello 2009 ²⁰²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=156)
Countries and setting	Conducted in Italy; Setting: Not stated

Study	Dell'agnello 2009 ²⁰²
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) All patients took part in an open-label, parent support phase. During this 6-week phase, parents received weekly standardised series of advice on the management of the behaviour problems of their children from psychologists. If patients did not have an improvement in CGI-S score of 2 or more, and at least a 30% decrease in the ADHD subscale score of investigator-rated SNAP-IV, they were randomised to the double blind phase (2) patients were required to have a score of at least 1.5 SD above the age norm for the ADHD subscale of the SNAP-IV, a CGI-S score of > 4 at both baseline and screening, a SNAP-IV ODD subscale score of at least 15, and a normal intelligence i.e. a score of >70 on an IQ test
Exclusion criteria	(1) Body weight <20 kg (2) history of bipolar disorder, psychosis, or seizure (other than febrile seizures) or past/concomitant intake of anticonvulsants for seizure control (3) risk of suicide (4) history of drug allergies (5) clinically significant cardiovascular disease (including hypertension) (6) patients taking antipsychotics, antidepressants, anticonvulsants, anorexics, anticoagulant (7) formal individual or family psychotherapy
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 9.9 years, Range : 6-15 years. Gender (M:F): 127:10. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (89% combined). 2. Age: Mixed (Children and young people 6-15 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: ODD (All participants diagnosed with ODD (DSM-IV)). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) (20% of the atomoxetine group and 12.5% of the placebo group had used previous drug therapy). 7. Severity: Not applicable / Not stated / Unclear (SNAP-IV score >1.5SD above norms for age and gender; CGI-S >=4).
Extra comments	Combined ADHD subtype=89%. Only 2 patients were excluded due to having a satisfactory response in the open label phase. However during this phase (before randomisation) 15 others dropped out due to subject/physician/sponsor/caregiver decisions and entry criteria exclusion.
Indirectness of population	Serious indirectness: 20% of the atomoxetine group and 12.5% of the placebo group had used previous drug therapy
Interventions	(n=105) Intervention 1: CNS stimulants - Atomoxetine. Once daily, morning administration. Patients were titrated over 7 days from 0.5 mg/kg/day to the target dose of 1.2 mg/kg/day. Duration 8 weeks. Concurrent medication/care: Not specified.

Study	Dell'agnello 2009²⁰²
	Further details: 1. Dose: 2. Method of titration: (n=32) Intervention 2: No treatment - Placebo. Duration 8 weeks. Concurrent medication/care: antipsychotics, Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE GROUP versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD subscale score of the SNAP-IV at 8 weeks; Group 1: mean -8.1 (SD 9.2); n=100, Group 2: mean -2 (SD 4.7); n=32; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Parent Rating Scale-revised: Short Form (CPRS-R:S) ADHD index at 8 weeks; Group 1: mean 23.1 (SD 7.1); n=100, Group 2: mean 28.3 (SD 5.6); n=32; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Teacher Rating Scale-revised: Short Form (CPRS-T:S) ADHD index at 8 weeks; Group 1: mean 21.8 (SD 8.9); n=100, Group 2: mean 28.4 (SD 6.1); n=32; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CGI-S (used to measure severity of symptoms) at 8 weeks; Group 1: mean 4.5 (SD 1); n=100, Group 2: mean 5.2 (SD 1); n=32; CGI-S 0-7 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ODD subscale score of the SNAP-IV at 8 weeks; Group 1: mean -2.7 (SD 4.1); n=100, Group 2: mean -0.3 (SD 2.6); n=32; SNAP-IV 0-54 or 0-18 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 8 weeks; Group 1: 3/105, Group 2: 0/32; Risk of bias: High; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: high risk of bias due to pre-randomisation administration of an intervention to select patients.
Study (subsidiary papers)	Dittmann 2011²⁰⁸ (Wehmeier 2011⁶⁵⁵)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=181)

Study (subsidiary papers)	Dittmann 2011 ²⁰⁸ (Wehmeier 2011 ⁶⁵⁵)
Countries and setting	Conducted in Germany; Setting: outpatients from 20 child and adolescent psychiatric and paediatric practices and hospitals throughout Germany
Line of therapy	Unclear
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR and DISYPS-KJ
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Comorbid ODD (only criteria A - C of DSM-IV-TR) or conduct disorder (DSM-IV-TR). If participants had started psychotherapy before study started they were included.
Exclusion criteria	Following all excluded: history of bipolar disorder (I or II), psychosis, pervasive developmental disorder or seizure disorder. Suicidal risk (determined by investigator). Possible requirement of psychotropic drugs.
Recruitment/selection of patients	patients recruited from November 2006 until November 2008 in a 3 to 28 day screening process
Age, gender and ethnicity	Age - Range: 6 to 17 years. Gender (M:F): 152:29. Ethnicity: Not stated
Further population details	1. ADHD subtype: All/mixed subtypes (~75% combined type). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Mixed line (including drug naive) (44.4% pre-treated with stimulant medication (mainly methylphenidate). Of these, 70% were switching due to inadequate response, 23.8% due to adverse events, 10% noncompliance and 10% patient decision (multiple responses)). 7. Severity:
Extra comments	The combined subtype was most frequent (76%) followed by the predominantly inattentive type (19.45%) and hyperactive/impulsive type (5%).
Indirectness of population	No indirectness
Interventions	<p>(n=60) Intervention 1: CNS stimulants - Atomoxetine. 1.2mg/kg. Fast titration (0.5mg/kg a day for 7 days followed by target dose). Study medication was given once in the morning. Duration 9 weeks. Concurrent medication/care: 3-28 day screening and washout period. Concomitant psychotherapy initiated before the study participation was acceptable. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=59) Intervention 2: No treatment - Placebo. Study medication was given once in the morning. Duration 9 weeks. Concurrent medication/care: 3-28 day screening and washout period. Concomitant psychotherapy initiated before the study participation was acceptable. Further details: 1. Dose: 2. Method of titration:</p>

Study (subsidiary papers)	Dittmann 2011²⁰⁸ (Wehmeier 2011⁶⁵⁵)
	<p>(n=61) Intervention 3: CNS stimulants - Atomoxetine. Slow titration (0.5mg/kg per day for 7 days, 0.8mg/kg for 7 days, followed by target dose of 1.2 mg/kg). Study medication was given once in the morning. Duration 9 weeks. Concurrent medication/care: 3-28 day screening and washout period. Concomitant psychotherapy initiated before the study participation was acceptable. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=121) Intervention 4: CNS stimulants - Atomoxetine. Slow titration (0.5mg/kg per day for 7 days, 0.8mg/kg for 7 days, followed by target dose of 1.2 mg/kg). 1.2mg/kg. Fast titration (0.5mg/kg a day for 7 days followed by target dose). Study medication was given once in the morning. Duration 9 weeks. Concurrent medication/care: 3-28 day screening and washout period. Concomitant psychotherapy initiated before the study participation was acceptable. Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Eli Lilly and Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE FAST TRITRATION GROUP versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV) for ADHD at 9 weeks; Group 1: mean 22.9 (SD 11.26); n=60, Group 2: mean 29.6 (SD 11.56); n=59; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 9 weeks; Group 1: 6/60, Group 2: 1/59; Risk of bias: Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE SLOW TRITRATION GROUP versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: Swanson, Nolan, and Pelham Rating Scale-Revised (SNAP-IV) for ADHD at 9 weeks; Group 1: mean 22.9 (SD 11.26); n=60, Group 2: mean 21.3 (SD 11.16); n=61; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 9 weeks; Group 1: 2/61, Group 2: 1/59; Risk of bias: Low; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Dittmann 2011²⁰⁸ (Wehmeier 2011⁶⁵⁵)
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome1: Very high due to attrition Protocol outcome 2: Low

Study (subsidiary papers)	Durell 2010-1²¹⁵ (Durell 2010-2²¹⁵)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=536)
Countries and setting	Conducted in USA; Setting: 32 outpatients sites in the US and Puerto Rico between August 2007 and February 2009
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Post-hoc subgroup analysis
Inclusion criteria	(1) Adults aged 18-30 years that met DSM-IV criteria for ADHD(2) CGI-S score of 4 or greater. (3) Concomitant current or lifetime diagnosis of specific phobias, generalised anxiety disorder or social anxiety disorder were allowed in the trial as well those with a history of dysthymia within 2 years of study screening.
Exclusion criteria	(1) Depression/anxiety (2) alcohol dependence (3) serious medical illness (4) actively using drugs of abuse.
Recruitment/selection of patients	Recruited from clinics and by advertisement.
Age, gender and ethnicity	Age - Other: The mean age of the younger adults (n=55) was 21.7 years and the older adults (n=481) was 43.4 years. Gender (M:F): 76/24. Ethnicity: 90% White, 5% Hispanic and 5% other
Further population details	1. ADHD subtype: All/mixed subtypes (78% combined subtype, 21.6% inattentive subtype and 0.45% hyperactive/impulsive subtype). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Not applicable / Not stated / Unclear. 7. Severity:
Extra comments	Comorbid conditions not reported
Indirectness of population	Serious indirectness: 14-21% of younger population have had previous treatment
Interventions	(n=26) Intervention 1: CNS stimulants - Atomoxetine. Administered morning and evening. Daily dose 60 mg;

Study (subsidiary papers)	Durell 2010-1 ²¹⁵ (Durell 2010-2 ²¹⁵)
	<p>patients with residual symptoms after 2 weeks increase to 90 mg and 120 mg after 4 weeks. Dosage could be decreased, or increase omitted if tolerability problems developed. Duration 10 weeks. Concurrent medication/care: An initial 1-week medication washout and evaluation period was in place. Previous stimulant exposure: 53.8% Further details: 1. Dose: 2. Method of titration:</p> <p>(n=29) Intervention 2: No treatment - Placebo. Placebo group. Duration 10 weeks. Concurrent medication/care: An initial 1-week medication washout and evaluation period was in place. Previous stimulant exposure: 72.4% Further details: 1. Dose: 2. Method of titration:</p> <p>(n=237) Intervention 3: CNS stimulants - Atomoxetine. Administered morning and evening. Daily dose 60 mg; patients with residual symptoms after 2 weeks increase to 90 mg and 120 mg after 4 weeks. Dosage could be decreased, or increase omitted if tolerability problems developed. Duration 10 weeks. Concurrent medication/care: An initial 1-week medication washout and evaluation period was in place. Previous stimulant exposure: 53.8% Further details: 1. Dose: 2. Method of titration:</p> <p>(n=244) Intervention 4: No treatment - Placebo. Placebo. Duration 10 weeks. Concurrent medication/care: An initial 1-week medication washout and evaluation period was in place. Previous stimulant exposure: 72.4% Further details: 1. Dose: 2. Method of titration:</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE YOUNGER ADULTS GROUP versus PLACEBO YOUNGER ADULTS</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: CAARS-Inv:SV (ADHD symptom score) - change at 10 weeks; Group 1: mean -11.77 (SD 7.3); n=26, Group 2: mean -8.38 (SD 9.4); n=29; CAARS-Inv:SV 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE OLDER ADULTS GROUP versus PLACEBO OLDER ADULTS GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p>	

Study (subsidiary papers)	Durell 2010-1²¹⁵ (Durell 2010-2²¹⁵)
	- Actual outcome: Conners Adult ADHD Rating Scale-Investigator Rated: Screening Version's (CAARS-Inv:SV) - change at 10 weeks; Group 1: mean -12.22 (SD 12.3); n=237, Group 2: mean -8.36 (SD 10.2); n=244; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study (subsidiary papers)	Durell 2013²¹⁶ (Durell 2014²¹⁷, Durrell 2014²¹⁸)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=445)
Countries and setting	Conducted in USA; Setting: 32 sites in the US and Puerto Rico
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who met DSM-IV criteria for ADHD, CGI-S score of 4 (moderate symptoms) or greater. Participants with concomitant current or lifetime phobias, general anxiety disorder or social anxiety disorder were allowed in the trial as well as patients with a history of dysthymia
Exclusion criteria	Patients with current major depression, panic disorder, post-traumatic stress disorder, an eating disorder, substance abuse or dependence, as well as current or lifetime obsessive-compulsive disorder, bipolar disorder or psychosis. Any participant who had a greater than 25% reduction in their ADHD symptoms as measured by the CAARS-Inv:SV Total ADHD symptoms score between visits 1 and 2 were also excluded
Recruitment/selection of patients	in the US and Puerto Rico between August 2007 and February 2009
Age, gender and ethnicity	Age - Range: 18-30 years. Gender (M:F): 225:190. Ethnicity: 75% white, 11.7% Hispanic, 8.5% African descent, 5% other
Further population details	1. ADHD subtype: All/mixed subtypes (78% of participants were diagnosed as having the combined DSM-IV

Study (subsidiary papers)	Durell 2013²¹⁶ (Durell 2014²¹⁷, Durrell 2014²¹⁸)
	ADHD subtype, 0.4% as the hyperactive/impulsive and 21.6% as the inattentive subtype). 2. Age: Adults 18-65 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (64% drug naive). 7. Severity: Mixed (Moderate to severe (inclusion criteria of CGI-S score of 4 or higher)).
Extra comments	78% of participants were diagnosed as having the combined DSM-IV ADHD subtype, 0.4% as the hyperactive/impulsive and 21.6% as the inattentive subtype
Indirectness of population	No indirectness
Interventions	(n=220) Intervention 1: CNS stimulants - Atomoxetine. Patients began treatment with 40 mg/d (dosed twice daily) for a minimum of 7 days. Following the last dose of 20 mg BID, the participants received 80 mg/d (dosed 40 mg BID) for a minimum of 7 days. At or after 5 weeks (visit 8), the dose could be increased to the maximum of 100 mg/d (dosed 50 mg BID, if the participants had residual symptoms in the judgement of the investigator. Duration 12 weeks. Concurrent medication/care: Participants underwent a washout period if they had been taking medications excluded by the study protocol Further details: 1. Dose: 2. Method of titration: (n=225) Intervention 2: No treatment - Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: Participants underwent a washout period if they had been taking medications excluded by the study protocol Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Company and /or one of its subsidiaries)

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

Protocol outcome 1: Quality of life at <3- or >6-months

- Actual outcome for Adult: Adult ADHD Quality of Life -29 (AAQOL-29) at 12 week; Group 1: mean 59.7 (SD 17.2); n=189, Group 2: mean 55.3 (SD 15.6); n=198; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adult: Behaviour Rating Inventory of Executive Function Adult version Self -Report (BRIEF-A) at 12 week; Group 1: mean 135.2 (SD 28.4); n=161, Group 2: mean 142.6 (SD 26.6); n=167; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: CGI-S at 12 week; Group 1: mean 3.7 (SD 1.2); n=192, Group 2: mean 4.1 (SD 1); n=200; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adult: Conners Adult Self-Report(CAARS-S:SV) at 12 week; Group 1: mean 24.3 (SD 11.8); n=189, Group 2: mean 28.5 (SD 10.6); n=197; Risk of bias: High; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Durell 2013²¹⁶ (Durell 2014²¹⁷, Durrell 2014²¹⁸)
Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at 12 week; Group 1: 21/220, Group 2: 6/225; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes at a high risk of attrition bias

Study	Escobar 2009²²⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Spain; Setting: 12 specialized outpatient settings within Spain.
Line of therapy	Unclear
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	DSM-IV-TR and K-SADS-PL
Stratum	Children
Subgroup analysis within study	Post-hoc subgroup analysis
Inclusion criteria	(1) 6-15 years (2) met DSM-IV criteria for ADHD (3) ADHD-RS-IV-Parent:Inv total score ≥ 1.5 SD above age norm for diagnostic subtype (4) newly diagnosed (≤ 3 months) (5) received no prior pharmacological treatment for ADHD.
Exclusion criteria	(1) Depression/anxiety, psychosis, pervasive developmental disorder (2) any relevant non-psychiatric condition (3) general impairment of intelligence (4) alcohol dependence (5) actively using drugs of abuse (6) involved with psychotherapy (7) medication with sympathomimetic activity (8) deemed to have difficulties following procedures or communicating with site personnel.
Recruitment/selection of patients	Referral by paediatricians or by families themselves for help with behavioural problems
Age, gender and ethnicity	Age - Mean (SD): 10.3 (2.5) years. Gender (M:F): 120:31. Ethnicity: Caucasian 96%, 4% not specified
Further population details	1. ADHD subtype: All/mixed subtypes (Combined 63%). 2. Age: Mixed (Children aged ≥ 6 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated, likely general population). 4. Comorbidities: Mixed (45.6% participants with a comorbidity (25.5% ODD, 16.8% tic disorder, 3.4% affective disorder,

Study	Escobar 2009²²⁰
	12.8% anxiety disorder)). 5. Diagnostic method: DSM (DSM-IV-TR (assessed using the K-SADS-PL)). 6. Line of treatment: 1st line (drug naive) (1st line). 7. Severity: Not applicable / Not stated / Unclear (Mean total baseline ADHD-RS-IV (parent) = approx 39).
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: CNS stimulants - Atomoxetine. 0.5 mg/kg per day first 2 weeks, 1.2 mg/kg per day for remaining 10 weeks. All doses were given once daily in the morning. Duration 12 weeks. Concurrent medication/care: After a 3-28 day screening and washout period, participants were randomised. Further details: 1. Dose: 2. Method of titration: (n=50) Intervention 2: No treatment - Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: After a 3-28 day screening and washout period, participants were randomised. Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Lilly Research Laboratories, Alcobendas, Spain)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE GROUP versus PLACEBO	
<p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Children (up to 18 years): CHIP-PRF (parents edition) - achievement subscale (adjusted mean change) at 12 weeks; Group 1: mean 4.94 (SD 13.03); n=99, Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV-Parent:Inv at 12 weeks; Group 1: mean 26.33 (SD 12.69); n=99, Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	<p>Protocol outcome 1 (Quality of life) High risk of bias due to high risk of outcome reporting bias (outcome was in the study protocol but not fully reported)</p> <p>Protocol outcome 2 (ADHD symptoms)</p>

Study	Escobar 2009²²⁰
	Low risk of bias

Study	Findling 2008²³⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=274)
Countries and setting	Conducted in USA; Setting: Multicentre trial in the US.
Line of therapy	Mixed line
Duration of study	Intervention time: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children ages 6-12 years diagnosed with ADHD according to the DSM-IV-TR (predominantly hyperactive/impulsive, inattentive, or combined type) were eligible for study inclusion. At screening, participants were required to have a Kaufman Brief Intelligence Test (KBIT) IQ score of >80, a total score of >26 on the ADHD Rating Scale-version IV
Exclusion criteria	Children with any comorbid psychiatric diagnosis (except ODD), a history of seizures during the last 2 years, a tic disorder, or any concurrent illness or skin disorder .Participants could not have taken clonidine, atomoxetine, antidepressants, anti-hypertensives, investigational medications
Recruitment/selection of patients	Following a 2 week screening period and up to 28 day medication washout if applicable, participants entered a 5 week double dummy dose optimisation period
Age, gender and ethnicity	Age - Range: 6-12 years. Gender (M:F): 187/95. Ethnicity: 77.3% white,14.5% African American, 0.7% Asian
Further population details	1. ADHD subtype: All/mixed subtypes (80.5% of the study population were of the combined subtype of ADHD, 17% of the inattentive subtype,1.4% of the hyperactive/impulsive subtype and 1.06% of the unclassified subtype). 2. Age: Children (6-12 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear (Only included oppositional defiant disorder). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (78% first line). 7. Severity:
Extra comments	80.5% of the study population were of the combined subtype of ADHD, 17% of the inattentive subtype, 1.4% of the hyperactive/impulsive subtype and 1.06% of the unclassified subtype. Participants with psychiatric comorbidities other than ODD were excluded

Study	Findling 2008 ²³⁴
Indirectness of population	No indirectness: Approximately 20% of the population had used previous treatment
Interventions	<p>(n=85) Intervention 1: No treatment - Placebo. Matching placebo to active treatments. Duration 5 weeks. Concurrent medication/care: Patients underwent up to 28 days medication washout period (if applicable) Further details: 1. Dose: 2. Method of titration:</p> <p>(n=98) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations) . Following a 2 week screening period, participants entered a 5 week dose optimization phase in which their treatments were optimised to 1 of 4 total daily dose strengths of Methylphenidate transdermal system (MTS)/placebo capsules. All participants received both a patch and capsule to be administered each day and all were initiated on the 10 mg/9 hour MTS. All treatments were administered at 7 am each morning and were assigned to participants. The dose was titrated over 5 weeks from 10mg/9hr to 15mg, 20mg and 30mg. Doses could be down-titrated at certain time points as deemed necessary by the investigator. Duration 5 weeks. Concurrent medication/care: Patients underwent up to 28 days medication washout period (if applicable) Further details: 1. Dose: 2. Method of titration: Titrated to optimum dose</p> <p>(n=91) Intervention 3: CNS stimulants - Methylphenidate (including modified-release preparations) . Following a 2 week screening period, participants entered a 5 week dose optimization phase in which their treatments were optimised to 1 of 4 total daily dose strengths of placebo transdermal system (PTS)/ OROS methylphenidate (MPH). All participants received both a patch and capsule to be administered each day and all were initiated on 18 mg OROS MPH. All treatments were administered at 7 am each morning and were assigned to participants. The dose was titrated over 5 weeks from 18mg to 27mg, 36mg and 54mg. Doses could be down-titrated at certain time points as deemed necessary by the investigator based on tolerability. Duration 5 weeks. Concurrent medication/care: Patients underwent up to 28 days medication washout period (if applicable) Further details: 1. Dose: 2. Method of titration: Titrated to optimum dose</p>
Funding	Study funded by industry (Shire Development Inc)

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

Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 5 weeks; Group 1: 2/91, Group 2: 1/85; Risk of bias: Low;

Indirectness of outcome: No indirectness

Study	Findling 2008 ²³⁴
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Behavioural outcomes at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Gadow 2008 ²⁵⁹ (Gadow 1995 ²⁶¹ ;Gadow 2007 ²⁶⁰)
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	1 (n=31)
Countries and setting	Conducted in USA; Setting: Tic Disorders Clinic, Stony Brook, New York
Line of therapy	Mixed line
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III or IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects had to meet DSM-III-R or DSM-IV diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette's syndrome.
Exclusion criteria	Children who exhibited one or more of the following were excluded from consideration for the study if (a) their tics were the major clinical management concern; (b) they were too severely ill (dangerous to self or others), psychotic, or mentally retarded (IQ < 70); or (c) had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive development disorder
Recruitment/selection of patients	Referrals from clinicians, schools, media advertisements, and parent support groups.
Age, gender and ethnicity	Age - Mean (SD): 8.95 (1.4). Gender (M:F): 25:6. Ethnicity: Caucasian 90%; 10% not stated
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (OCD, Tourette's and tic disorder, OCD). 5. Diagnostic method: DSM (DSM-III or IV). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness

Study	Gadow 2008 ²⁵⁹ (Gadow 1995 ²⁶¹ ;Gadow 2007 ²⁶⁰)
Interventions	<p>(n=71) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . 0.1mg/kg twice daily, administered approximately 3.5 hours apart, 7 days a week. Duration 2 weeks. Concurrent medication/care: All medication was stopped at least one week before the study began Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=71) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations) . 0.3mg/kg twice daily, administered approximately 3.5 hours apart, 7 days a week. Duration 2 weeks. Concurrent medication/care: All medication was stopped at least one week before the study began Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=71) Intervention 3: CNS stimulants - Methylphenidate (including modified-release preparations) . 0.5mg/kg twice daily, administered approximately 3.5 hours apart, 7 days a week. Max dose 20mg. Duration 2 weeks. Concurrent medication/care: All medication was stopped at least one week before the study began Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=71) Intervention 4: No treatment - Placebo. Placebo. Duration 2 weeks. Concurrent medication/care: All medication was stopped at least one week before the study began Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (Supported in part by a research grant from the Tourette syndrome Association, Inc and P.H.S. grant from the National Institute of Mental Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 0.1MG versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Abbreviated Teachers Rating Scale at 2 weeks; Group 1: mean 8 (SD 6); n=71, 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: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): Abbreviated Parent Rating Scale at 2 weeks; Group 1: mean 8.2 (SD 5.1); n=71, 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: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): IOWA Conners Inattention-Overactivity scale at 2 weeks; Group 1: mean 5.2 (SD 3.5); n=71, Group 2: mean 7.4 (SD 6.9); n=71

Risk of bias: All domain - High, Selection - Low, Blinding - Low, 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	Gadow 2008 ²⁵⁹ (Gadow 1995 ²⁶¹ ;Gadow 2007 ²⁶⁰)
<p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): IOWA Conners Oppositional-Defiant scale at 2 weeks; Group 1: mean 1.9 (SD 2.8); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 0.3MG versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Abbreviated Teachers Rating Scale at 2 weeks; Group 1: mean 7.3 (SD 5.8); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children (up to 18 years): Abbreviated Parent Rating Scale at 2 weeks; Group 1: mean 10 (SD 5.5); n=71, Group 2: mean 11 (SD 7); n=71 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children (up to 18 years): IOWA Conners Inattention-Overactivity scale at 2 weeks; Group 1: mean 4.7 (SD 3.4); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): IOWA Conners Oppositional-Defiant scale at 2 weeks; Group 1: mean 1.7 (SD 2.8); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 0.5MG versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Abbreviated Teachers Rating Scale at 2 weeks; Group 1: mean 5.7 (SD 5.1); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children (up to 18 years): Abbreviated Parent Rating Scale at 2 weeks; Group 1: mean 7.8 (SD 4.7); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children (up to 18 years): IOWA Conners Inattention-Overactivity scale at 2 weeks; Group 1: mean 3.8 (SD 3.1); n=71, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p>	

Study	Gadow 2008 ²⁵⁹ (Gadow 1995 ²⁶¹ ;Gadow 2007 ²⁶⁰)
<p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): IOWA Conners Oppositional-Defiant scale at 2 weeks; Group 1: mean 1.1 (SD 1.9); n=71, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Gau 2007 ²⁶⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=106)
Countries and setting	Conducted in Taiwan; Setting: Three outpatient sites in Taiwan, including one national and two private medical centres.
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) a total score on the ADHD Rating Scale-IV-Parent version: Investigator Administered and scored (ADHDRS-IV) of at least 25 for boys or 22 for girls, or greater than 12 for their diagnostic subtype at both visit 1 and visit 2; (2) A Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) score \geq 4 at both visit 1 and visit 2; (3) normal intelligence as judged by investigators; and (4) no ADHD treatment medication, or completion of washout procedures before entering the study.
Exclusion criteria	Subjects were excluded if they weighed less than 20 kg or more than 60 kg; had a serious medical illness, such as cardiovascular disease; had a history of bipolar I or II disorder, psychosis, or pervasive development disorder; had anxiety disorder; had a history of any seizure disorder or prior electroencephalogram (EEG) abnormalities related to epilepsy, or had taken (or were taking anticonvulsants for seizure control; history of alcohol or drug abuse within the past 3 months; use of other psychoactive medications

Study	Gau 2007 ²⁶⁶
Recruitment/selection of patients	Eligible if they met the (DSM-IV) diagnostic criteria for ADHD, confirmed by the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version (K-SADS-E)
Age, gender and ethnicity	Age - Range: 6-16 years. Gender (M:F): 47:6. Ethnicity: Taiwanese (not clearly specified)
Further population details	1. ADHD subtype: All/mixed subtypes (73% combined, 27% inattentive). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed (16% ODD, 8% CD). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (Less than 50% drug naive). 7. Severity: Mixed (CGI-S score of 4 or higher).
Extra comments	Co-morbid conditions: ODD (16%), CD (8%)
Indirectness of population	No indirectness
Interventions	<p>(n=72) Intervention 1: CNS stimulants - Atomoxetine. Once daily morning dose. Mean total daily dose at 43.13mg (SD = 17.27), ranging from 16.48 to 99 mg. Week 1 0.8mg/kg per day for 4 days, week 2 increased to 1.2mg/kg. Week 3 decreased or maintained based on clinical judgement. Another dose adjustment could be done to a maximum of 1.8mg/kg, time frame not specified but at visit 5. (At the time this was the maximum dose - the product label now indicates 1.4mg/kg). Duration 6 weeks. Concurrent medication/care: 56.9% previously on psychostimulants (name of intervention not specified) Further details: 1. Dose: 2. Method of titration:</p> <p>(n=34) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: 58.8% previously on psychostimulants Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Eli & Lilly Co., Taiwan)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS-IV at 6 weeks; Group 1: mean 36.7 (SD 6.7); n=69, Group 2: mean 37.1 (SD 6.4); n=29; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): CGI-ADHD-S at 6 weeks; Group 1: mean 5.3 (SD 0.8); n=72, Group 2: mean 5.2 (SD 0.8); n=72; CGI-ADHD-RS 1-7 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: --
- Actual outcome for Children (up to 18 years): Conners' Teacher Rating Scale (Revised: Short Form) at 6 weeks; Group 1: mean 28.6 (SD 14.8); n=69, Group 2: mean 35 (SD 17.8); n=29; CTRS 0-84 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Conners' Parent Rating Scale (Revised: Short Form) at 6 weeks; Group 1: mean 44.7 (SD 12.9); n=69, Group 2: mean 42.6 (SD 15.4); n=29; CPRS 0-81 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Gau 2007 ²⁶⁶
	<ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS-IV Hyperactivity/impulsivity subscale at 6 weeks; Group 1: mean -8.7 (SD 5.5); n=69, Group 2: mean -4.1 (SD 6.9); n=29; ADHD-RS subscale 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV inattention subscale at 6 weeks; Group 1: mean -8.7 (SD 6.1); n=69, Group 2: mean -5.2 (SD 7.2); n=29; ADHD-RS subscale 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R:S Inattention subscale at 6 weeks; Group 1: mean -3.3 (SD 3.6); n=69, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R:S hyperactivity/impulsivity subscale at 6 weeks; Group 1: mean -3.1 (SD 3.3); n=69, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CTRS-R:S hyperactivity/impulsivity subscale at 6 weeks; Group 1: mean -2.3 (SD 4.8); n=69, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CTRS-R:S inattention subscale at 6 weeks; Group 1: mean -0.8 (SD 3); n=69, Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 6 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: high risk of attrition bias Protocol outcome 2: low risk of bias

Study	Geller 2007 ²⁷¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=176)
Countries and setting	Conducted in USA; Setting: 15 sites including sites associated with Massachusetts General Hospital, Dartmouth-Hitchcock Medical Center, and Mt Sinai Medical Center
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children (up to 18 years)

Study	Geller 2007 ²⁷¹
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects who met DSM-IV criteria for ADHD and for at least one of the following anxiety disorders: separation anxiety disorder, generalised anxiety disorder, or social phobia.
Exclusion criteria	Significant abnormalities in baseline laboratory or electrocardiogram results; met diagnostic criteria for current posttraumatic stress disorder, panic disorder, specific phobias, or obsessive compulsive disorder; scored ≥ 15 on the Children's Yale-Brown Obsessive Compulsive Scale; or had a history of hypertension or bipolar, psychotic, pervasive developmental, or seizure disorders. Patients in the following categories were excluded: pregnant and lactating females, users of monoamine oxidase inhibitors within 2 weeks of visit 2, recent substance abusers, and individuals at serious risk or with medical or personal conditions likely to affect the trial or health outcomes. Concomitant use of the drugs that inhibit the CYP2D6 enzyme pathway were not permitted due to potential interactions.
Recruitment/selection of patients	By referral and advertisement
Age, gender and ethnicity	Age - Range: 8-17. Gender (M:F): 114:62. Ethnicity: White (82%)
Further population details	1. ADHD subtype: All/mixed subtypes (Combined (75%), Inattentive (23%), Hyperactive (1%)). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=87) Intervention 1: CNS stimulants - Atomoxetine. Doses were initiated at 0.8 mg/kg/day for 3 days and increased to the target dose of approximately 1.2 mg/kg/day. At visit 6 or thereafter the dose could be increased to 1.8 mg/kg/day for patient with significant residual ADHD symptoms. The daily dose could not exceed 120 mg, regardless of weight. Duration 12 weeks. Concurrent medication/care: Patients taking methylphenidate or amphetamine for the treatment of ADHD could continue taking these medications until 2 days before visit 2. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=89) Intervention 2: No treatment - Placebo. The placebo group received placebo twice daily. Duration 12 weeks. Concurrent medication/care: Patients taking methylphenidate or amphetamine for the treatment of ADHD could continue taking these medications until 2 days before visit 2. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry

Study	Geller 2007 ²⁷¹
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Treatment response (defined as $\geq 25\%$ reduction from baseline on ADHDRS-IV-PI) at 12 weeks; Group 1: 54/64, Group 2: 10/69; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 12 weeks; Group 1: 1/64, Group 2: 1/69; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Low risk of bias

Study	Ghuman 2009 ²⁷⁴
Study type	RCT (Patient randomised; Crossover: no washout reported)
Number of studies (number of participants)	1 (n=17)
Countries and setting	Conducted in USA; Setting: The study was conducted at the University of Arizona
Line of therapy	2nd line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not stratified but pre-specified: Children with Pervasive Developmental Disorder (PDD)
Inclusion criteria	Participants were 3- to 5-year-old pre-schoolers who met the DSM-IV-TR criteria for autistic disorder (AD), Asperger disorder, or PDD Not Otherwise Specified (NOS) supported by the Autism Diagnostic Interview–Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS), or for developmental delays defined by intelligence quotient (IQ) and/or Vineland Adaptive Behavior Scales (VABS) composite score of below 70 \square 5. Subjects were included only if they exhibited impairing symptoms of hyperactivity and impulsivity in multiple settings (e.g., home, school, or other community places, such as Sunday school,

Study	Ghuman 2009 ²⁷⁴
	library, restaurant) for at least 6 months. The pre-schoolers also had to meet severity criteria based on the Hyperactive-Impulsive subscale T-score of 65, 1.5 standard deviation (SD) (93rd percentile) above the age- and sex-adjusted mean on either the Conners' Parent Rating Scale–Revised or Conners' Teacher Rating Scale– Revised (CPRS-R or CTRS-R) (Conners 2001). Impairment criteria included a score of 60 or below on the Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983) and a score of moderate or above on the Clinical Global Impressions–Severity (CGI-S) scale (Guy 1976).
Exclusion criteria	Exclusion criteria were: (1) Prior failed treatment with MPH defined as a minimum of 5 weeks of MPH at 15mg=day for children weighing ≤ 18.0 kg and 20 mg=day for children weighing >18.0kg at the time of entering the study; (2) concurrent medications having central nervous system (CNS) effects (including any psychotropic medications); (3) history of tics; (4) major medical condition that could be affected negatively by MPH; and (5) diagnosis of bipolar disorder, psychosis, significant suicidality, or other psychiatric disorders requiring treatment with additional medication.
Recruitment/selection of patients	Participants were recruited through referrals from paediatricians, pre-school teachers, and interested parents in response to study flyers, media advertising, and word of mouth.
Age, gender and ethnicity	Age - Mean (SD): 4.8 (1.0)Range= 3-5 years. Gender (M:F): 13/1. Ethnicity: 64.3% Caucasian and 35.7% Hispanic
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not reported). 2. Age: Pre-schoolers (<6 years) 3. At risk population: General population 4. Comorbidities: Mixed (Autism (35.71%), PDD (50%), Intellectual disability (14.29%)). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (8 children were drug naive and 6 had received past trials of psychotropic medications). 7. Severity: Not applicable / Not stated / Unclear
Extra comments	Co-morbid psychiatric disorders included oppositional defiant disorder (ODD) in 3 children (21.4%), separation anxiety disorder in 2 children (14.3%), and adjustment disorder in 1 child (7.1%).
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . MPH was administered in gel capsules and was initiated at 1.25 mg b.i.d; subsequent dose adjustments were made weekly during clinic visits based on clinical impression until an optimal dose that produced the maximal effect with minimal side effects was reached. Sometimes, the dose was titrated at a slower rate if the pre-schooler experienced moderate adverse event. Following a week long single-blind titration, each child entered a 4-week double-blind crossover phase with 2 weeks of placebo and 2 weeks of the child's "best dose" in random order— either placebo–MPH or MPH–placebo. Duration 2 weeks. Concurrent medication/care: Con- current medications during the trial included a 2-day course of prednisone and albuterol inhaler for asthma, flonase nasal spray for nasal congestion, and atropine eye drops for lazy eye in 1 child each. Melatonin was added during the study for sleep problems in 3 children. Further details: 1. Dose: 2. Method of titration:

Study	Ghuman 2009 ²⁷⁴
	(n=17) Intervention 2: No treatment - Placebo. Matching placebo. Duration 2 weeks. Concurrent medication/care: Con- current medications during the trial included a 2-day course of prednisone and albuterol inhaler for asthma, flonase nasal spray for nasal congestion, and atropine eye drops for lazy eye in 1 child each. Melatonin was added during the study for sleep problems in 3 children. Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding (National Institute of Mental Health grant K23 MH01883 and Arizona Institute of Mental Health Research grants to J.K.G.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH GROUP versus PLACEBO GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Conners' Parent Rating Scale-Revised-DSM-IV-ADHD Subscale-PDD subgroup at 4 weeks; Group 1: mean 21.83 (SD 8.06); n=7, Group 2: mean 30.75 (SD 9.18); n=7

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 ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): Nisonger Child Behavior Rating Form-Parent-Hyperactive Subscale-Entire Developmental Disorder sample at 4 weeks; Group 1: mean 10.5 (SD 3.78); n=7, Group 2: mean 14.14 (SD 6.75); n=7

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 ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): Conners' Parent Rating Scale-Revised-DSM-IV-ADHD Subscale-Entire Developmental Disorder sample at 4 weeks;

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 ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): Nisonger Child Behavior Rating Form-Parent-Hyperactive Subscale-PDD subgroup at 4 weeks; Group 1: mean 10.5 (SD 3.83); n=7, Group 2: mean 14.14 (SD 6.75); n=7

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 ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Children (up to 18 years): Clinical Global Impressions (CGI)-Global Improvement score-Clinician-PDD subgroup at 4 weeks; Group 1: mean 1.75 (SD 1.14); n=7, Group 2: mean 3 (SD 1.04); n=7

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Ghuman 2009 ²⁷⁴
	<p>- Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome for Children (up to 18 years): Clinical Global Impressions (CGI)-Global Improvement score-Clinician-Entire DD Sample at 4 weeks; Group 1: mean 1.71 (SD 10.7); n=7, Group 2: mean 2.79 (SD 1.12); n=7</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome for Children (up to 18 years): CGI- Severity of Illness score-Clinician-PDD subgroup at 4 weeks; Group 1: mean 4.42 (SD 0.79); n=7, Group 2: mean 5 (SD 0.74); n=7; CGI- Severity of Illness score-Clinician 0-7 Top=High is poor outcome</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome for Children (up to 18 years): CGI- Severity of Illness score-Clinician-Entire DD sample at 4 weeks; Group 1: mean 4.36 (SD 0.74); n=7, Group 2: mean 4.86 (SD 0.77); n=7</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome for Children (up to 18 years): Children's Global Assessment Scale-PDD subgroup at 4 weeks; Group 1: mean 54.33 (SD 6.85); n=7, Group 2: mean 49.5 (SD 5.05); n=7</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome for Children (up to 18 years): Children's Global Assessment Scale-Entire DD sample at 4 weeks; Group 1: mean 55.14 (SD 6.63); n=7, Group 2: mean 51.86 (SD 7.62); n=7</p> <p>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 ; Baseline details: there were no significant differences in the age, gender, or CPRS-R-DSM-IV-ADHD subscale scores; Group 1 Number missing: ; Group 2 Number missing:</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Ginsberg 2012 ²⁸¹
Study type	RCT (Patient randomised; Parallel)

Study	Ginsberg 2012 ²⁸¹
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Sweden; Setting: All inmates were hosted at Norrtälje Prison, a high-security prison outside Stockholm, Sweden, for long-term, adult male inmates, typically convicted of violent or drug-related crimes.
Line of therapy	1st line
Duration of study	Intervention time: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Eligible participants were adult male prison inmates, aged 21–61 years, with ADHD according to DSM-IV criteria and had to agree not to behave violently during the study (2) Participants with comorbid disorders such as autism-spectrum disorder, anxiety and depression could take part if they were considered to be stable at baseline (3) previous drug-elicited episodes of psychosis were not a cause for exclusion, other than chronic psychoses (4) concurrent medication not interfering with methylphenidate was permitted for treating comorbid disorders, as long as doses were stable for at least 1 month at baseline (5) medications interfering with methylphenidate had to be tapered off before the baseline visit took place.
Exclusion criteria	(1) Participants known to be non-responsive or intolerant to methylphenidate, or intolerant to lactose. (2) Evidence of substance misuse up to 3 months before baseline, assessed in urine samples (3) intellectual disability, epilepsy, glaucoma, uncontrolled hypertension, angina pectoris, cardiac arrhythmias, cardiac abnormality or a family history of serious cardiac illnesses. Hepatitis C without liver insufficiency did not preclude inclusion.
Recruitment/selection of patients	Participants were initially selected on the basis of the ADHD questionnaires, with diagnosis subsequently confirmed in comprehensive assessments by experienced board-certified psychiatrists and clinical psychologists. Participants were mainly recruited from Stockholm County, and had at least 14 months left until conditional release to ensure completion of the trial.
Age, gender and ethnicity	Age - Range: 21–61 years. Gender (M:F): 30/0. Ethnicity: Not specified
Further population details	1. ADHD subtype: Combined (93% were of the combined subtype of ADHD, 7% were predominantly inattentive subtype). 2. Age: Adults 18-65 years) (Aged 21-61 years). 3. At risk population: Secure estate (Secure estates). 4. Comorbidities: Mixed (Participants with co-morbid disorders such as ASD, anxiety and depression were included if they were stable at baseline. All reported lifetime substance use disorder; all but one had antisocial personality disorder.). 5. Diagnostic method: DSM (The structured clinical interview for DSM-IV Axis I Disorders (SCID-I), the Hare Psychopathy checklist, a self-rated version of the SCID-I and a structured interview). 6. Line of treatment: 1st line (drug naive) (16.7% had previously been treated with

Study	Ginsberg 2012 ²⁸¹
	MPH. None of the inmates were known to be non-responsive or intolerant to MPH.). 7. Severity: Severe (Baseline scores on CAARS-O:SV, ASRS, CGI-S and GAF show participants had severe ADHD).
Extra comments	23.3% of the study population reported lifetime psychiatry co-morbidity of autism-spectrum disorder, 73% reported mood and anxiety disorder, 100% reported conduct disorder, 97% had antisocial personality disorder and 10% demonstrated psychotherapy as a comorbidity. All participants had a lifetime substance use disorder
Indirectness of population	Serious indirectness: 14% have had previous treatment
Interventions	<p>(n=15) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Osmotic-release oral system (OROS) methylphenidate was titrated from 36 mg/day for 4 days to 54 mg/day for 3 days and then to 72 mg/day for the remaining 4 weeks. Duration 5 weeks. Concurrent medication/care: Concurrent medication not interfering with methylphenidate was permitted for treating comorbid disorders, as long as doses were stable for at least 1 month at baseline. Medications interfering with methylphenidate had to be tapered off before the baseline visit took place. Further details: 1. Dose: Not applicable / Not stated / Unclear (72mg/day). 2. Method of titration: Fixed dose (Titrated to fixed dose of 72mg/day).</p> <p>(n=15) Intervention 2: No treatment - Placebo. Matching Placebo. Duration 5 weeks. Concurrent medication/care: Concurrent medication not interfering with methylphenidate was permitted for treating comorbid disorders, as long as doses were stable for at least 1 month at baseline. Medications interfering with methylphenidate had to be tapered off before the baseline visit took place. Further details: 1. Dose: 2. Method of titration:</p>
Funding	Academic or government funding (Swedish Ministry of Health and Social Affairs and Stockholm Council, Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH versus PLACEBO GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: Self-reported ADHD Symptoms Total score (Adult self-report scale) at 5 weeks; Group 1: mean 36.8 (SD 13.2); n=15, Group 2: mean 54.7 (SD 9.78); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: CGI-S ADHD at 5 weeks; Group 1: mean 4.1 (SD 0.22); n=15, Group 2: mean 5.7 (SD 0.69); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: >25% reduction in ADHD Symptoms Total score (Conners' Adult ADHD Rating Scale) at 5 weeks; Group 1: 13/15, Group 2: 0/15; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Ginsberg 2012 ²⁸¹
Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Global Assessment of Functioning at 5 weeks; Group 1: mean 55.2 (SD 13.4); n=15, Group 2: mean 39.4 (SD 6.91); n=15; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Goodman 2016 ²⁸⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=357)
Countries and setting	Conducted in USA; Setting: 35 clinical sites in the US
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Between July 2009 and February 2010
Age, gender and ethnicity	Age - Range: 18 to 65 years. Gender (M:F): Define. Ethnicity: 82% white, 11% black, 6% Asian, 1% other
Further population details	1. ADHD subtype: All/mixed subtypes (81% combined, 17% inattentive, 2% hyperactive/impulsive). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Moderate (AISRS score of above 24).
Indirectness of population	No indirectness
Interventions	(n=178) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) .

Study	Goodman 2016²⁸⁶
	<p>Subjects were given 18mg/day of MPH which could be increased at each subsequent 3 weekly visits to 36mg, 54mg and 72mg until the participant reached an AISRS score of less than 18 or a limit of tolerability. Mean (SD) daily dose was 54.89mg(15.75mg). Duration 6 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose</p> <p>(n=179) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Ortho-McNeil Janssen Scientific Affairs)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: AISRS total scores at 6 weeks; Group 1: mean -17.1 (SD 12.44); n=174, Group 2: mean -11.7 (SD 13.3); n=175; AISRS ? Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37; Group 2 Number missing: 41</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Drop out due to adverse events at 6 weeks; Group 1: 8/178, Group 2: 5/179 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 37; Group 2 Number missing: 41</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Goto 2013²⁸⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=391)
Countries and setting	Conducted in Japan; Setting: 45 study sites in Asia

Study	Goto 2013 ²⁸⁷
Line of therapy	Mixed line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) additional historical diagnosis of ADHD during childhood (2) score of 2 or more on at least 6 items of either the inattentive or hyperactive/impulsive subscales of CAARS)3_ CGI-S score of 4 or more
Exclusion criteria	(1) bipolar disorder (2) schizophrenia (3) depressive disorder or any current anxiety disorder
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 32.2(8). Gender (M:F): 185:203. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (48.7% combined, 49.2% inattentive, 2.1% hyperactive/impulsive). 2. Age: Adults 18-65 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (21.9% had prior stimulant exposure). 7. Severity: Mixed (CGI-S score of 4 or more).
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	<p>(n=195) Intervention 1: CNS stimulants - Atomoxetine. Initiated at 40mg a day and increased to 80mg 2 weeks later. Depending on response, this could be increased to 105mg and 120mg at 2 week intervals. Patients were discontinued if they were unable to tolerate 80mg/day. Duration 10 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose</p> <p>(n=196) Intervention 2: No treatment - Placebo. No details given . Duration 10 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Eli Lilly)

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

Study	Goto 2013 ²⁸⁷
Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: AAQoL at 10 weeks; Group 1: mean 12.8 (SD 15.9); n=193, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: CAARS total score at 10 weeks; Group 1: mean -14.3 (SD 10.4); n=191, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS Inattention subscale at 10 weeks; Group 1: mean -8.2 (SD 6); n=191, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS Hyperactivity subscale at 10 weeks; Group 1: mean -6.1 (SD 5.3); n=191, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: BRIEF-A at 10 weeks; Group 1: mean -10.7 (SD 13.6); n=193, Group 2: mean -6.1 (SD 10.4); n=195; BRIEF-A 0-100 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at 10 weeks; Group 1: 10/195, Group 2: 3/196; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of bias

Study	Greenhill 2002 ²⁹²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=321)
Countries and setting	Conducted in USA; Setting: 32 centres in the US
Line of therapy	Mixed line
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)

Study	Greenhill 2002 ²⁹²
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ADHD combined subtype or predominantly hyperactive-impulsive subtype as defined by DSM-IV (2) Blood pressure, heart rate, oral temperature within normal range
Exclusion criteria	(1) comorbid psychiatric diagnosis (2) history of seizure or tic disorder or family history of Tourette's (3) IQ below 80 (4) females who had undergone menarche (5) use of amphetamines, pemoline or an investigational drug within 30 days of the study entry (6) concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or CNS (7) hyperthyroidism or glaucoma (8) any acute or chronic illness or disability that could confound the study results (9) children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to methylphenidate, or were living with anyone who currently had substance abuse disorder
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 6 to 16 years. Gender (M:F): 157: 57. Ethnicity: 71% White, 15% Black, 10% Hispanic, 4% Other
Further population details	1. ADHD subtype: All/mixed subtypes (Hyperactive/impulsive and combined subtypes). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (64% had been previously treated for ADHD). 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=155) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . Children took placebo tablets for 1 week prior to treatment. If symptoms did not response to placebo, children were randomised to 20mg methylphenidate for 1 week. After this, investigators judged the adequacy of the dosage response, and were continued on the dose if response was adequate and they tolerated treatment. If the child had room for improvement, they were titrated up to 40mg in week 2 or 60mg in week 3. Duration 3 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration: (n=159) Intervention 2: No treatment - Placebo. Placebo. Duration 3 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Celltech Pharmaceuticals Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE

Study	Greenhill 2002 ²⁹²
PREPARATIONS) versus PLACEBO	
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-I responders (score of 1 or 2) at 3 weeks; Group 1: 125/154, Group 2: 78/156 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17; Group 2 Number missing: 28</p> <p>Protocol outcome 2: Serious adverse events at All - Actual outcome for Children (up to 18 years): Serious Adverse events at 3 weeks; Group 1: 0/155, Group 2: 0/159 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17; Group 2 Number missing: 28</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 3 weeks; Group 1: 2/155, Group 2: 0/159 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17; Group 2 Number missing: 28</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Hamedi 2014 ³⁰⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Iran; Setting: Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran)
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	None specified
Exclusion criteria	(1) Any chronic medical condition such as cardiovascular disease, epilepsy and brain organic disease (2) Substance abuse or dependence during last 6 months (3) ☐ Pregnancy or breastfeeding (4) IQ of <75 (5) Unstable psychiatric state (e.g. suicide, aggression, (6) Any psychotropic medication usage currently (7) Any usage of methylphenidate, atomoxetine, amphetamines or other ADHD medications in the last 3 months (8) bipolar disorder
Recruitment/selection of patients	Outpatients who were referred to a psychiatrist for psychiatric evaluation, between January 2013 to March 2014.
Age, gender and ethnicity	Age - Range: 20 to 60 years. Gender (M:F): 27:15. Ethnicity: 100% Persian
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not specified). 2. Age: Adults 18-65 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear (Not specified). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear. Any usage of methylphenidate, atomoxetine, amphetamines or other ADHD medications in the last 3 months was an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Previous treatment not specified
Interventions	(n=21) Intervention 1: Bupropion . Each patient was randomly assigned to receive treatment either with bupropion (starting with 75mg/day to a maximum of 150mg/day). The average dose of bupropion administered for cases was 150mg/d. No further details. Duration 6 weeks. Concurrent medication/care: Not specified

	<p>Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose</p> <p>(n=21) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: No details</p> <p>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration:</p>
Funding	Academic or government funding (Tehran University of Medical Sciences)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: CAARS final values at 6 weeks; Group 1: mean 23.71 (SD 15.34); n=21, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Subtype, comorbidities, previous treatment not specified; Group 1 Number missing: ; Group 2 Number missing:</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	NCT00844753 trial: Handen 2015³⁰⁸
Study type	RCT (Site randomised; Parallel)
Number of studies (number of participants)	1 (n=128)
Countries and setting	Conducted in USA; Setting: multicentre trial in 3 US sites (University of Pittsburgh Medical Centre, Ohio State University, University of Pittsburgh and University of Rochester)
Line of therapy	Unclear

Study	NCT00844753 trial: Handen 2015 ³⁰⁸
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years): Children with ASD+ADHD symptoms
Subgroup analysis within study	Not applicable
Inclusion criteria	All study participants underwent a complete assessment to establish diagnosis of autistic disorder, pervasive developmental disorder – not otherwise specified (PDD-NOS), or Asperger’s disorder based upon the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV-TR). Participants had a minimum mental age of 24 months and demonstrated significant symptoms of overactivity and/or inattention at both home and school based on a mean item score >1.50 on the parent and teacher completed SNAP scales and CGI-S >4.
Exclusion criteria	Rett disorder, childhood disintegrative disorder, lifetime diagnosis of schizophrenia or other psychotic disorder, bipolar disorder or current diagnosis of depression/OCD. Other exclusion criteria included a prior adequate trial of ATX (minimum of at least 4 weeks within the last 2 years), regular usage of beta adrenergic blocking agents, asthma medicine and prior involvement in a highly structured parent training program
Recruitment/selection of patients	from January 2009 to April 2014, participants were screened at the participating sites
Age, gender and ethnicity	Age - Mean (SD): 8.1 (2.1) Range=5-14 years. Gender (M:F): 109/19. Ethnicity: White 82%, African American 7.8%, 8% multiracial and 2% other
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (not reported). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Mixed line (including drug naive) (55% drug naive although unsure if this includes children taking melatonin). 7. Severity:
Extra comments	Patients underwent an ASD diagnostic assessment and cognitive assessment. Both parents and teachers completed behaviour rating scales to confirm symptoms and assess levels of non-compliance. Patients were enrolled irrespective of severity of non-compliance scores. Co-morbid conditions not reported
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: CNS stimulants - Atomoxetine. Once study eligibility was established, participants were randomised to 1 of 4 treatment arms. Dose adjustments were made at week 6. Families assigned to Parent Training (PT) met weekly for 1:1 sessions with a PT clinician for 60-90 minutes. Final dose= 49.8 (23.3) mg. Duration 10 weeks. Concurrent medication/care: Participants were free of psychotropic medications (with the exception of melatonin or low dose clonidine i.e < 0.3 mg/day for sleep) for 2 weeks before study randomisation. A single anticonvulsant for seizure control was allowed provided that stable doses and seizure free status had been six months or more.

Study	NCT00844753 trial: Handen 2015 ³⁰⁸
	<p>Further details: 1. Dose: 2. Method of titration:</p> <p>(n=32) Intervention 2: Combination - See description. Atomoxetine (ATX) + Parent Training (PT). Once study eligibility was established, participants were randomised to 1 of 4 treatment arms. Dose adjustments were made at week 6. Families assigned to Parent Training (PT) met weekly for 1:1 sessions with a PT clinician for 60-90 minutes. Final dose= 40.0 (18.4) mg. Duration 10 weeks. Concurrent medication/care: Participants were free of psychotropic medications (with the exception of melatonin or low dose clonidine i.e < 0.3 mg/day for sleep) for 2 weeks before study randomisation. A single anticonvulsant for seizure control was allowed provided that stable doses and seizure free status had been six months or more. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=32) Intervention 3: Combination - See description. Placebo (PLA) + Parent Training (PT). Once study eligibility was established, participants were randomised to 1 of 4 treatment arms. Dose adjustments were made at week 6. Families assigned to Parent Training (PT) met weekly for 1:1 sessions with a PT clinician for 60-90 minutes. Final dose= 42.4 (14.3) mg. Duration 10 weeks. Concurrent medication/care: Participants were free of psychotropic medications (with the exception of melatonin or low dose clonidine i.e < 0.3 mg/day for sleep) for 2 weeks before study randomisation. A single anticonvulsant for seizure control was allowed provided that stable doses and seizure free status had been six months or more. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=32) Intervention 4: Combination - See description. Placebo. Once study eligibility was established, participants were randomised to 1 of 4 treatment arms. Final dose= 45.6 (20.3) mg. Duration 10. Concurrent medication/care: Participants were free of psychotropic medications (with the exception of melatonin or low dose clonidine i.e < 0.3 mg/day for sleep) for 2 weeks before study randomisation. A single anticonvulsant for seizure control was allowed provided that stable doses and seizure free status had been six months or more. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=64) Intervention 5: No treatment - Placebo. Combination of two placebo arms. Duration 10 weeks. Concurrent medication/care: Participants were free of psychotropic medications (with the exception of melatonin or low dose clonidine i.e < 0.3 mg/day for sleep) for 2 weeks before study randomisation. A single anticonvulsant for seizure control was allowed provided that stable doses and seizure free status had been six months or more. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=64) Intervention 6: Combination - See description. Two ATX treatment arms. Duration 10 weeks. Concurrent medication/care: Participants were free of psychotropic medications (with the exception of</p>

Study	NCT00844753 trial: Handen 2015³⁰⁸
	melatonin or low dose clonidine i.e < 0.3 mg/day for sleep) for 2 weeks before study randomisation. A single anticonvulsant for seizure control was allowed provided that stable doses and seizure free status had been six months or more. Further details: 1. Dose: 2. Method of titration:
Funding	Equipment / drugs provided by industry (Trial was supported from the National Institute of mental Health to Ohio State University, University of Pittsburgh and University of Rochester)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATX GROUP versus PLA GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Parent Swanson, Nolah and Pelham Score (SNAP)-Total ADHD score at 10 week; Group 1: mean 1.24 (SD 0.56); n=29, Group 2: mean 1.74 (SD 0.86); n=21; SNAP 0-3 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 3, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other

- Actual outcome for Children (up to 18 years): Parent Swanson, Nolah and Pelham Score (SNAP)-Inattention score at 10 week; Group 1: mean 1.45 (SD 0.71); n=25, Group 2: mean 1.79 (SD 0.84); n=21

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 3, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other

- Actual outcome for Children (up to 18 years): Parent Swanson, Nolah and Pelham Score (SNAP)-Hyperactivity score at 10 week; Group 1: mean 1.15 (SD 0.74); n=29, Group 2: mean 1.69 (SD 0.97); n=21

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 3, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other

Study	NCT00844753 trial: Handen 2015 ³⁰⁸
	<p>- Actual outcome for Children (up to 18 years): Teacher Swanson, Nolam and Pelham Score (SNAP)-Total ADHD score (LEAST SQUARE MEAN) at 10 week; Group 1: mean 1.49 (SD 0.74); n=29, Group 2: mean 1.44 (SD 0.85); n=21 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 3, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other</p> <p>- Actual outcome for Children (up to 18 years): Teacher Swanson, Nolam and Pelham Score (SNAP)-Inattention score (LEAST SQUARE MEAN) at 10 week; Group 1: mean 1.66 (SD 0.78); n=29, Group 2: mean 1.63 (SD 0.98); n=21 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 3, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other</p> <p>- Actual outcome for Children (up to 18 years): Teacher Swanson, Nolam and Pelham Score (SNAP)-Hyperactivity score (LEAST SQUARE MEAN) at 10 week; Group 1: mean 1.32 (SD 0.92); n=29, Group 2: mean 1.25 (SD 0.92); n=21 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 3, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATX TREATMENT GROUPS versus PLACEBO GROUPS</p>	
	<p>Protocol outcome 1: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): study dropout due to adverse event at 10 week; Group 1: 11/53, Group 2: 18/46 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ATX assignment was double blind however PT assignment was rater-single blind (family, behavior therapist and study co-ordinator were aware of assignment) but other study personnel remained blinded; Indirectness of outcome: No indirectness ; Baseline details: difference in ethnicity, baseline CGI-s scores; Group 1 Number missing: 11, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other; Group 2 Number missing: 18, Reason: inadequate improvement, behavioural adverse event, physical adverse event, lost to follow up, unable to swallow medicine, other</p>

Study	NCT00844753 trial: Handen 2015³⁰⁸
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Harfterkamp 2012³¹⁵ (Harfterkamp 2014³¹⁴)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=97)
Countries and setting	Conducted in Netherlands; Setting: Child and adolescent psychiatry centres (6 in total, 3 university and 3 non university)
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) diagnosis of ADHD and ASD (2) intelligence of at least IQ 60 (3) ADI-R scores above the cut-off for ADF (above 10 on the social interaction subscale, 8 for verbal subjects, 7 for nonverbal subjects, above 3 on restricted and repetitive behaviour subscale). (4) ADHD DSM-IV scores at least 1.5SD above the age norm for children's diagnostic subtype.
Exclusion criteria	(1) Weight of less than 20kg (2) psychosis, bipolar disorder, substance abuse, serious medical illness, history of seizures (3) ongoing use of psychoactive medications other than the study drug (4) intended start of psychotherapy or inpatient treatment. All other comorbidities were allowed. Prior experience with ADHD medication was not an exclusion criteria.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 6 to 17 years. Gender (M:F): 83:14. Ethnicity: 99% White, 1% African
Further population details	1. ADHD subtype: All/mixed subtypes (Not specified). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: ASD 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (Less than 50% drug naive). 7. Severity: Not applicable / Not stated / Unclear (ADHD DSM-IV scores at least 1.5SD above the age norm for children's diagnostic subtype.).
Extra comments	ADHD and ASD

Study (subsidiary papers)	Harfterkamp 2012 ³¹⁵ (Harfterkamp 2014 ³¹⁴)
Indirectness of population	No indirectness
Interventions	<p>(n=48) Intervention 1: CNS stimulants - Atomoxetine. Titrated in 3 weeks to a fixed once daily dose of 1.2mg/kg per day (first week, 0.5mg/kg per day, second week 0.8mg/kg per day, third week 1.2mg/kg per day). Capsules were identical to placebo. Atomoxetine capsules were 5,10,20,25 or 40mg. All doses were given as two capsules taken together in the morning. Duration 8 weeks. Concurrent medication/care: Participants starting other psychoactive medication other than the study drug, or had structured psychotherapy or inpatient treatment had to discontinue Further details: 1. Dose: 2. Method of titration:</p> <p>(n=49) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Participants starting other psychoactive medication other than the study drug, or had structured psychotherapy or inpatient treatment had to discontinue Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Eli Lilly and Company)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS total change scores (adjusted for treatment, visit, baseline values - MMRM) at 8 weeks ; Group 1: mean 31.6 (SD 8.3); n=48, Group 2: mean 38.3 (SD 8.2); n=49; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS inattention subscore change scores (adjusted for treatment, visit, baseline values - MMRM) at 8 weeks ; Group 1: mean 17.2 (SD 4.4); n=48, Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS hyperactivity-impulsivity subscore change scores (adjusted for treatment, visit, baseline values - MMRM) at 8 weeks ; Group 1: mean 14.5 (SD 5.1); n=48, Group 2: mean 18.4 (SD 4.8); n=49; ADHD-RS-IV 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): CGI-ADHD-I scores (dichotomised) at 8 weeks ; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Conners Teachers Rating Scale (Revised, short form) ADHD score - adjusted for baseline at 8 weeks ; Group 1: mean 15.1 (SD 7.4); n=48, Group 2: mean 17.8 (SD 7.3); n=49; CTRS-R:S ADHD score ? Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Conners Teachers Rating Scale (Revised, short form) oppositional score - adjusted for baseline at 8 weeks ; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): Conners Teachers Rating Scale (Revised, short form) hyperactivity score - adjusted for baseline at 8 weeks ; Risk of bias: High; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Harfterkamp 2012 ³¹⁵ (Harfterkamp 2014 ³¹⁴)
	- Actual outcome for Children (up to 18 years): Conners Teachers Rating Scale (Revised, short form) cognitive/attention score - adjusted for baseline at 8 weeks ; Risk of bias: High; Indirectness of outcome: No indirectness
	Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 8 weeks ; Group 1: 1/48, Group 2: 0/49; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias (other than protocol outcome 2)

Study	Huss 2015 ³⁴⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=338)
Countries and setting	Conducted in Multiple countries; Setting: 58 centres across 11 European countries, the USA and Canada.
Line of therapy	Unclear
Duration of study	Intervention time: 10-13 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: 6 to 17 years
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ADHD_RS-IV score of at least 32 and a minimum score on CGI-S of 4 (2) age appropriate intellectual functioning (3) normal cardiac functioning for age sex and height
Exclusion criteria	(1) pregnant females or noncompliance with protocol contraception requirements (2) any clinically significant illness (3) current comorbid psychiatric diagnosis except for ODD (4) family history of cardiac abnormalities (5) history of alcohol or substance abuse (6) tics disorder
Recruitment/selection of patients	Between January 2011 to May 2013
Age, gender and ethnicity	Age - Range: . Gender (M:F): 249:89. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (85% combined, 12% inattentive and 3% hyperactive impulsive). 2.

Study	Huss 2015 ³⁴⁰
	Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed (88% no comorbidities). 5. Diagnostic method: Not applicable / Not stated / Unclear 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Moderate (ADHD-RS-IV score of 32 or higher).
Indirectness of population	No indirectness
Interventions	<p>(n=115) Intervention 1: Guanfacine. The first 4 weeks was a dose optimization period followed by a 6 week maintenance period and a 2 week tapering off period. The duration was 10 weeks for children between 6 to 12 years and 13 weeks for older children, in order to allow participants to reach optimum doses of up to 0.12mg/kg per day. Tablets for administers in 1,2,3 and 4mg; children were initiated at 1mg/day and increased by mg increments after a minimum of 1 week and to a maximum of 4,5,6 or 7mg/day if between 34 and 41,4, 41.5 and 49.4, 49.5 and 58.4, and 58.5 and 91kg, respectively. Duration 10 - 13 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear (Mean 3.6(1.3)mg). 2. Method of titration: Titrated to optimum dose</p> <p>(n=112) Intervention 2: CNS stimulants - Atomoxetine. The first 4 weeks was a dose optimization period followed by a 6 week maintenance period and a 2 week tapering off period. The duration was 10 weeks for children between 6 to 12 years and 13 weeks for older children, in order to allow participants to reach optimum doses of up to 0.12mg/kg per day. Dose was initiated at 0.5mg/kg per day in those weighing less than 70kg and increased to the approximate target of 1.2mg/kg per day, and if well tolerated after 1 week increased to 1.4mg per kg per day. In those weighing more than 70kg dosage was initiated at 40mg per day and increased to 80mg per day and increased after 1 week to 100mg per day if required. Mean dose was 42.1(20.1)mg. Duration 10 - 13 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed (42.1(20.1)mg per day mean). 2. Method of titration: Titrated to optimum dose</p> <p>(n=111) Intervention 3: No treatment - Placebo. Placebo. Duration 10 to 13 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p>
Funding	Study funded by industry (Shire Development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus ATOMOXETINE

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Children (up to 18 years): CGI-I score of 1 or 2 at 10 to 13 weeks; Group 1: 76/114, Group 2: 63/112

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Study	Huss 2015 ³⁴⁰
	<p>Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV total scores at 10 to 13 weeks; Group 1: mean -23.9 (SD 12.41); n=113, Group 2: mean -18.6 (SD 11.91); n=112; ADHD-RS-IV 0-54 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 10 to 13 weeks; Group 1: 9/115, Group 2: 5/112 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 ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-I score of 1 or 2 at 10 to 13 weeks; Group 1: 76/115, Group 2: 49/111 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV total scores at 10 to 13 weeks; Group 1: mean -23.9 (SD 12.41); n=114, Group 2: mean -15 (SD 13.07); n=111; ADHD-RS 0-54 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 10 to 13 weeks; Group 1: 9/115, Group 2: 1/111 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 ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-I score of 1 or 2 at 10 to 13 weeks; Group 1: 63/112, Group 2: 49/111 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcomedata - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23</p>

Study	Huss 2015 ³⁴⁰
<p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV total scores at 10 to 13 weeks; Group 1: mean -18.6 (SD 11.91); n=112, Group 2: mean -15 (SD 13.07); n=111; ADHD-RS-IV 0-54 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 23</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 10 to 13 weeks; Group 1: 5/112, Group 2: 1/111 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 ; Group 1 Number missing: 24; Group 2 Number missing: 23</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Jain 2011 ³⁴⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in USA; Setting: 40 study sites across USA
Line of therapy	2nd line
Duration of study	Intervention time: 4 weeks intervention plus 1 week screening and 1 week washout period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR criteria
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 6-12 years old. Met DSM-IV-TR criteria for ADHD. Had ADHD-RS-IV score of ≥ 28 at baseline after washout. Prior ADHD treatment was discontinued before washout period. Non-remitters to methylphenidate treatment.
Exclusion criteria	None detailed
Recruitment/selection of patients	Subgroup of larger study

Study	Jain 2011 ³⁴⁸
Age, gender and ethnicity	Age - Mean (SD): 9 years old. Gender (M:F): 15 (58%) Male, 11 (42%) female. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Subtype not specified). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear (Comorbidities not specified). 5. Diagnostic method: DSM (DSM-IV-TR criteria). 6. Line of treatment: 2nd line (non-response to CNS stimulants) (Nonremitter to methylphenidate treatment). 7. Severity: Mixed (ADHD-RS \geq 28).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Randomised equally to either 30 mg/day for 4 weeks, 30 mg/day for week 1 and 50 mg/day for weeks 2-4, 30 mg/day for week 1 and 50 mg/day for week 2 and 70 mg/day for weeks 3-4. Duration 4 weeks. Concurrent medication/care: 1 week washout period before LDX treatment. Further details: 1. Dose: Mixed (Varied dose from 30 mg/day to 70 mg/day depending on randomisation). 2. Method of titration: Fixed dose (Varied dose from 30 mg/day to 70 mg/day depending on randomisation). (n=7) Intervention 2: No treatment - Placebo. Placebo for 4 weeks. Duration 4 weeks. Concurrent medication/care: 1 week washout period before LDX treatment. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose
Funding	Study funded by industry (Funded by Shire Canada Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Clinical response: \geq 30% reduction in ADHD-RS-IV total score and CGI-I of 1 or 2 at 4 weeks; Group 1: 15/19, Group 2: 3/7

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Baseline details: Aged 6-12 years old, nonremitters to MPH treatment, ADHD-RS-IV score \geq 28; Blinding details: Investigator and the patient (and his/her parent/guardian) were blinded to treatment; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Serious adverse events at All

- Actual outcome for Children (up to 18 years): Serious adverse events at 4 weeks; Group 1: 0/19, Group 2: 0/7

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Baseline details: Aged 6-12 years old, nonremitters to MPH treatment, ADHD-RS-IV score \geq 28; Blinding details: Investigator and the patient (and his/her parent/guardian) were blinded to treatment; Group 1 Number missing: ; Group 2 Number missing:

Study	Jain 2011 ³⁴⁸
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Jahangard 2017 ³⁴⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in Iran; Setting:
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 (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	1) the scores of the Conners Parent rating scale revised - long version was 70 and higher, 2) based on the structured interview a psychiatrist diagnosed ADHD and symptoms of ODD according to DSM-IV, 3) a previous standard treatment with MPH (10-15mg/d) failed within the first 3-5 weeks of treatment, 4) family counselling sessions (2-4 sessions within the first 3-5 weeks) to cope with the child's symptoms of ADHD and ODD failed to show improvements, 5) age was between 8 and 12 years, 6) no other serious medical or psychiatric disorders such as epilepsy, autism, mental retardation, eating disorders, depressive or anxiety disorders were diagnosed, and 7) behavioural observations, parents information on child's history and school reports from the past 6 months were also taken into account.
Exclusion criteria	Not stated.
Recruitment/selection of patients	Children were recruited from the children's frashchian hospital, hamadan university of medical sciences, Hamadan (Iran) during late spring to summer 2014.
Age, gender and ethnicity	Age - Mean (SD): 8.557 (1.204). Gender (M:F): 62 male, 22 female. Ethnicity: Not stated.
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Children (6-12 years) (7.28-9.95). 3. At risk population: General population 4. Comorbidities: ODD 5. Diagnostic method: DSM 6. Line of treatment: 2nd line (non-response only, mixed treatment) (Children were enrolled in the study, if previous treatments with standard

Study	Jahangard 2017³⁴⁶
	dosages of MPH (10-15mg/d) and family counselling failed to show improvements). 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Antipsychotics - Risperidone. MPH and Risperidone (0.5 mg/d). Tablets of risperidone and placebo were identical in shape, colour, size, texture and scent. Duration 8 weeks. Concurrent medication/care: All participants were on methylphenidate (1 mg/kg/d), Ritalin, sustained. Further details: 1. Dose: 2. Method of titration: Fixed dose (0.5mg/d). (n=42) Intervention 2: No treatment - Placebo. MPH and placebo. Tablets of risperidone and placebo were identical in shape, colour, size, texture and scent. Duration 8 weeks. Concurrent medication/care: All participants were on methylphenidate (1 mg/kg/d), Ritalin, sustained. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Other (The entire study has been performed without external funding.)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Cognitive problems/inattention - Conners Parent Rating Scale Revised - Long Version (CPRS) at 8 weeks PT; Group 1: mean 1.79 (SD 0.3); n=42, Group 2: mean 2.02 (SD 0.33); n=42

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 (up to 18 years): Hyperactivity - Conners Parent Rating Scale Revised - Long Version (CPRS) at 8 weeks PT; Group 1: mean 1.62 (SD 0.23); n=42, Group 2: mean 1.67 (SD 0.24); n=42

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: Behavioural outcomes at <3- or >6-months

- Actual outcome for Children (up to 18 years): Oppositional problems - Conners Parent Rating Scale Revised - Long Version (CPRS) at 8 weeks PT; Group 1: mean 1.71 (SD 0.29); n=42, Group 2: mean 1.92 (SD 0.27); n=42

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 3: Emotional dysregulation at <3- or >6-months

- Actual outcome for Children (up to 18 years): Social problems - Conners Parent Rating Scale Revised - Long Version (CPRS) at 8 weeks PT; Group 1:

Study	Jahangard 2017 ³⁴⁶
	mean 1.77 (SD 0.41); n=42, Group 2: mean 2.04 (SD 0.41); n=42 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 outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months

Study	Jain 2011 ³⁵⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=236)
Countries and setting	Conducted in USA; Setting: 13 centres in the USA
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ADHD diagnosis of the hyperactive or combined subtype (2) Minimum score of 26 on the ADHD RS IV
Exclusion criteria	(1) Females of childbearing age who refused to use birth control (2) any clinically significant illness or abnormality that would increase the safety risk of clonidine (3) clinically significant abnormalities on ECGs (4) any diagnosis or history of a psychiatric disorder that required psychotropic medication and patients with a severe concomitant axis II or II disorder that could interfere with assessment (5) history of conduct disorders, syncopal episodes, seizures (6) use of any investigational drug within 30 days of the study or had positive drug tests for any medications other than those used to treat ADHD
Recruitment/selection of patients	From October 2007 to August 2008
Age, gender and ethnicity	Age - Range: 6 to 17 years. Gender (M:F): 165:63. Ethnicity: 60% White, 28% Black, 6% Hispanic/Latino, 6% unspecified
Further population details	1. ADHD subtype: All/mixed subtypes (combined or hyperactive/impulsive subtypes). 2. Age: Mixed (Mean age 9.5). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Moderate

Study	Jain 2011 ³⁵⁰
	(Minimum score of 26 on ADHD-RS-IV).
Indirectness of population	No indirectness
Interventions	<p>(n=158) Intervention 1: Clonidine. Patients were randomly assigned to receive clonidine 0.2mg per day or 0.4mg per day. A forced dose escalating titration schedule of 0.1mg per day per week was used to achieve the target dose for the patient, followed by dose tapering in 0.1mg per day per week intervals until cessation of treatment at the end of week 8. Patients who experiences adverse events that warranted dose reduction were discontinued from the study. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose</p> <p>(n=78) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Addrenex Pharmaceuticals)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS IV total scores at 5 weeks; Group 1: mean -16.06 (SD 13.27); n=158, Group 2: mean -7.5 (SD 9.41); n=78; ADHD RS 0-54 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 52; Group 2 Number missing: 35

- Actual outcome for Children (up to 18 years): ADHD-RS IV hyperactivity scores at 5 weeks; Group 1: mean -8.362 (SD 7.034); n=152, Group 2: mean -4.1 (SD 7); n=76; ADHD RS 0-54 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 52; Group 2 Number missing: 35

- Actual outcome for Children (up to 18 years): ADHD-RS IV inattention scores at 5 weeks; Group 1: mean -7.7 (SD 7.122); n=152, Group 2: mean -3.4 (SD 6.58); n=76; ADHD RS subscale 0-27 Top=High is poor outcome

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 52; Group 2 Number missing: 35

Protocol outcome 2: Serious adverse events at All

- Actual outcome for Children (up to 18 years): Serious adverse events at 5 weeks; Group 1: 0/158, Group 2: 0/78

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Study	Jain 2011 ³⁵⁰
Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 5 weeks; Group 1: 20/158, Group 2: 1/78 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Jafarinia 2012 ³⁴⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Iran; Setting: Outpatient child and adolescent psychiatry clinics at Roozbeh Psychiatric Hospital
Line of therapy	1st line
Duration of study	Intervention time: 6 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Children and adolescents aged 6-17 years who met the DSM-IV-TR diagnostic criteria for ADHD (2) total and/or subscale scores on ADHD-RS-IV School version of at least 1.5 standard deviations (SD"s) above norms for patients age and gender (3) prior to entry, the diagnosis of ADHD was confirmed by a child and adolescent psychiatrist. At screening, the clinicians conducted a psychiatric assessment based on the DSM-IV-TR criteria for ADHD, the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview and performed a thorough medical evaluation
Exclusion criteria	(1) Psychiatric comorbidities (excluding ODD) (2) high risk of suicide (3) intellectual disability (4) any clinically important chronic medical condition such as epilepsy
Recruitment/selection of patients	Outpatient clinics from May 2010 to November
Age, gender and ethnicity	Age -- Range: 6-17 years. Gender (M:F): 13/31. Ethnicity: All Persian
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (not reported). 2. Age: Mixed (Children and young

Study	Jafarinia 2012 ³⁴⁵
	people (6 to 17 years)). 3. At risk population: Looked after children 4. Comorbidities: Not applicable / Not stated / Unclear (Comorbidities not specified). 5. Diagnostic method: DSM 6. Line of treatment: 1st line (drug naïve) (All naïve). 7. Severity: Not applicable / Not stated / Unclear (Possibly excluding mild? 1.5 standard deviations above norms for patient's age and gender).
Extra comments	Subtypes of ADHD not reported. None of the patients had the diagnosis of co-morbid ODD disorder.
Indirectness of population	No indirectness
Interventions	<p>(n=20) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). MPH 20-30 mg/day depending on weight (20 mg/day for <30 kg) and 30 mg/day for >30 kg). MPH was titrated up during the trial according to the following schedule: 10 mg/day (5 mg in the morning and 5 mg at midday) in week 1; 20 mg/day (10 mg in the morning and 10 mg at midday) in week 2; 20 mg/day for children < 30 kg and 30 mg/day for children > 30 kg. (10 mg in the morning, 10 mg at midday and 10 mg at 16:00) in week 3 and thereafter. Mean dosage at weeks 6 were 25.5mg/day. Duration 6 weeks. Concurrent medication/care: None reported. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=20) Intervention 2: Bupropion. 50 mg capsules 100-150 mg/day depending on weight (100 mg/day for patients < 30 kg and 150 mg/day for patients > 30 kg. Bupropion was started at 50 mg for patients <30 kg and 75 mg for patients > 30 kg and then titrated up to 100 mg/day for patients < 30 kg and 150 mg/day for patients >30 kg. Duration 6 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p>
Funding	Academic or government funding (Tehran University of Medical Sciences (grant number 9745))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION GROUP versus MPH GROUP

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Teacher -Hyperactivity at 6 weeks; Group 1: mean -3.8 (SD 5.1); n=20, Group 2: mean -3.9 (SD 4.8); n=20; ADHD-RS hyperactivity subscale 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Parent Response (50% reduction in scores) at 6 weeks; Group 1: 18/20, Group 2: 15/20; Risk of bias: Low; Indirectness of outcome: Serious indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Parent -Total Score at 6 weeks; Group 1: mean -24.8 (SD 7.3); n=20, Group 2: mean -26.2 (SD 8.1); n=20; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Parent -Inattention at 6 weeks; Group 1: mean -11.4 (SD 3.8); n=20, Group 2: mean -12.4 (SD 3.7); n=20; Risk of bias: --; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Parent -Hyperactivity at 6 weeks; Group 1: mean -13.3 (SD 4.6); n=20, Group 2: mean -13.9

Study	Jafarinia 2012 ³⁴⁵
	<p>(SD 5.6); n=20; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Teacher -Total Score at 6 weeks; Group 1: mean -7.8 (SD 8.5); n=20, Group 2: mean -7.3 (SD 10.5); n=20; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Teacher -Inattention at 6 weeks; Group 1: mean -3.9 (SD 6); n=20, Group 2: mean -3.5 (SD 5.7); n=20; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: --; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS-IV-Teacher -Hyperactivity at 6 weeks; Group 1: mean -3.9 (SD 4.8); n=20, Group 2: mean -3.8 (SD 5.1); n=20; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Serious adverse events at All</p> <p>- Actual outcome for Children (up to 18 years): Serious adverse events at 6 weeks; Group 1: 0/20, Group 2: 0/20; Risk of bias: ; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): Drop out due to adverse events at 6 weeks; Group 1: 0/20, Group 2: 0/20; Risk of bias: Low; Indirectness of outcome: No indirectness</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: low risk of bias

Study	Kahbazi 2009 ³⁶¹
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=46)
Countries and setting	Conducted in Iran; Setting: Roozbeh psychiatric hospital
Line of therapy	Unclear
Duration of study	Intervention time: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD-RS-IV score of at least 1.5 SDs above norms.

Study	Kahbazi 2009 ³⁶¹
Exclusion criteria	(1) Current or history of pervasive developmental disorders, schizophrenia or other psychiatric disorders (2) current psychiatric disorders that require drugs (3) any evidence of suicidal risk or intellectual disabilities (4) other chronic medical conditions excluded, including organic brain disorder, seizures (5) current abuse or dependence on drugs in the last 6 months (6) hypertension or hypotension (7) habitual consumption of more than 250 mg/day of caffeine.
Recruitment/selection of patients	From December 2005 to March 2007
Age, gender and ethnicity	Age – Range: 6 to 15 years. Gender (M:F): 35:11 . Ethnicity: All Persian
Further population details	1. ADHD subtype: Combined (All patients with combined subtype). 2. Age: Mixed (Children and young people (aged 6-15 years; mean age approx. 9 years)). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Not applicable / Not stated / Unclear (Most comorbidities excluded). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: Not applicable / Not stated / Unclear (Not stated). 7. Severity: Not applicable / Not stated / Unclear (ADHD-RS-IV total or subscale scores > 1.5SD compared to norms for age and gender. Mean baseline scores approximately 36).
Extra comments	ADHD combined type
Indirectness of population	Serious indirectness: Unclear if participants have previously received medication for ADHD
Interventions	(n=23) Intervention 1: CNS stimulants – Modafinil. Once daily 200-300 mg per day depending on weight (200 mg/day for <30kg and 300 mg/day for >30kg). Titration process: week 1 100 mg/day, week 2 200 mg/day, week 3 300 mg/day (for children weighing >30 kg). Duration 6 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration: (n=23) Intervention 2: No treatment – Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration:
Funding	Other author(s) funded by industry (Tehran University of Medical Sciences)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS-Parent scale change scores at 6 weeks; Group 1: mean -22.47 (SD 8.92); n=23, Group 2: mean -8.21 (SD 6.15); n=23; ADHD-RS-parent scale 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-RS-Teacher scale change scores at 6 weeks; Group 1: mean -23.26 (SD 8.15); n=23, Group 2: mean -7.69 (SD 5.04); n=23; ADHD-RS-teacher scale 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Kahbazi 2009 ³⁶¹
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: low risk of bias

Study	Kelsey 2004 ³⁶⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=197)
Countries and setting	Conducted in USA; Setting: 12 outpatient sites in the US
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ADHD diagnosis confirmed by K-SADS-L (2) 1.5SDs above gender and age norms on ADHD-RS
Exclusion criteria	(1) serious medical illness (2) history of psychosis or bipolar disorder (3) alcohol or drug abuse within the past 3 months (4) ongoing use of psychoactive medication other than the study drug
Recruitment/selection of patients	Patients were recruited via advertisements and referrals.
Age, gender and ethnicity	Age - Range: 6 to 12 years. Gender (M:F): 139: 58. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (69% combined, 3% hyperactive/impulsive and 28% inattentive). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (35% ODD). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (52% had previous stimulant exposure). 7. Severity: Not applicable / Not stated / Unclear (1.5SDs above gender and age norms on ADHD-RS).
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	(n=133) Intervention 1: CNS stimulants - Atomoxetine. Single daily dose in the morning. Patients began on

Study	Kelsey 2004³⁶⁶
	<p>0.8mg/kg per day for 3 days, followed by 1.2mg/kg per day for the remainder of the first week. The daily dose was then increased after 4 weeks if required, to a maximum of 1.8mg/kg per day. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose</p> <p>(n=64) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Eli Lilly)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHDRS inattention subscale at 8 weeks; Group 1: mean -8.3 (SD 8); n=133, Group 2: mean -4.1 (SD 6.1); n=64 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26; Group 2 Number missing: 17 - Actual outcome for Children (up to 18 years): ADHDRS hyperactive/impulsive subscale at 8 weeks; Group 1: mean -8.5 (SD 7.5); n=133, Group 2: mean -2.9 (SD 5.8); n=64 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26; Group 2 Number missing: 17 - Actual outcome for Children (up to 18 years): ADHDRS total score at 8 weeks; Group 1: mean -16.7 (SD 14.5); n=126, Group 2: mean -7 (SD 10.8); n=60; ADHD-RS 0-54 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26; Group 2 Number missing: 17</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 8 weeks; Group 1: 6/133, Group 2: 1/64 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Kollins 2011 ³⁷⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	6 week (n=178)
Countries and setting	Conducted in USA; Setting: 9 sites in the US
Line of therapy	Unclear
Duration of study	Intervention time: 6 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Stratified then randomised: stratified by age category (6-12 years and 13-17 years) and site
Inclusion criteria	Male and female subjects 6-17 years meeting DSM-IV-TR criteria for a diagnosis of ADHD, a baseline score of >24 on the ADHD-RS-IV and a baseline score > 4 on the CGI-S scale were enrolled.
Exclusion criteria	Any current co-morbid psychiatric diagnosis (except ODD), weight <25 kg, any cardiac condition, or a Pediatric Daytime Sleepiness Scale (PDSS) score >22 at screening and/or baseline.
Recruitment/selection of patients	9 sites in the US from May to October 2005. After confirmation of eligibility at the baseline visit
Age, gender and ethnicity	Age - Mean (SD): 12.6 (2.81) Range=6-17 years. Gender (M:F): 124/54. Ethnicity: White 66.9%, Black 16.3% and Hispanic 12.4%
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (71.9% had used psychostimulants in the 12 months before the study start). 7. Severity:
Extra comments	74.7% of the study population were combined subtype of ADHD, 23.6% of the population was of the inattentive subtype and 1.7% of the population
Indirectness of population	No indirectness
Interventions	(n=121) Intervention 1: Guanfacine. The dose optimisation phase started at a dose of 1 mg/day. The dose was increased in 1 mg/ week increments to a maximum of 3 mg/day based on overall clinical response and tolerability. Patients were administered individually titrated dose in the morning. Duration 6 weeks. Concurrent medication/care: A washout period before study reported although no details provided. Further details: 1. Dose: 2. Method of titration: (n=57) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 6 weeks. Concurrent medication/care: A washout period before study reported although no details provided. Further details: 1. Dose: 2. Method of titration:

Study	Kollins 2011 ³⁷⁸
Funding	Study funded by industry (Shire Development Inc)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GXR GROUP versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS-IV total score at 6 weeks; Group 1: mean -18 (SD 10.72); n=114, Group 2: mean -11.9 (SD 13.12); n=54; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Inattentive scale at 6 weeks; Group 1: mean -8.8 (SD 5.98); n=114, Group 2: mean -5.5 (SD 7.23); n=54; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Hyperactivity/impulsivity scale at 6 weeks; Group 1: mean -9.2 (SD 5.83); n=114, Group 2: mean -6.5 (SD 6.68); n=54; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Much improved or very much improved on CGI-I at 6 weeks; Group 1: 65/114, Group 2: 19/54; Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Adverse events leading to discontinuation at 6 weeks; Group 1: 1/114, Group 2: 1/54; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Kooij 2004 ³⁸⁵
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Netherlands; Setting: Outpatient clinic of GGZ Delfland in Delft, Netherlands
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Semi-structured diagnostic interviews for ADHD and co-morbid disorders based on DSM-IV criteria

Study	Kooij 2004 ³⁸⁵
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	All ADHD types were eligible; subjects with co-morbid psychiatric disorders were included, unless these disorders required to be treated first or when treatment with methylphenidate was contra-indicated.
Exclusion criteria	Subjects with clinically significant medical conditions, abnormal baseline laboratory values, a history of tic disorders, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions (i.e. suicidal behaviours, psychosis, mania, physical aggression, currently ongoing substance abuse), current use of psychotropics, prior use of methylphenidate or amphetamines
Recruitment/selection of patients	Subjects were self-referred or referred by other clinicians
Age, gender and ethnicity	Age - Range: 20-56. Gender (M:F): 24:21. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Adults 18-65 years) (20-56). 3. At risk population: General population 4. Comorbidities: Mixed (Mood disorders (n=28), anxiety disorders (n=34), SUDs (n=37), bulimia nervosa (n=3)). 5. Diagnostic method: DSM (Semi-structured diagnostic interviews for ADHD and co-morbid disorders based on DSM-IV criteria). 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=45) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Medication was dispensed in tablets of 10mg, it was prescribed in four or five times a day dosing, dosing was adjusted to five times a day when rebounding occurred. Study medication was titrated up from low to high doses to avoid exposure to high initial doses and minimise side effects. Treatment began at 0.5 mg/kg/day by week 1, followed by 0.75 mg/kg/day by week 2 and up to 1 mg/kg/day by week 3 unless adverse effects emerged. Duration 3 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=45) Intervention 2: No treatment - Placebo. Identical placebo tablets were dispensed by the study pharmacy. Duration 3 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (The Board of Scientific Activities (WAC) of the Reiner de Graaf Hospital)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IMMEDIATE RELEASE MPH versus PLACEBO	
Protocol outcome 1: ADHD symptoms at <3- or >6-months	

Study	Kooij 2004 ³⁸⁵
	- Actual outcome for Adult: Treatment response at 3 weeks; Group 1: 17/45, Group 2: 3/45; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinued due to adverse events at 3 weeks; Group 1: 0/45, Group 2: 0/45; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Kratochvil 2005 ³⁸⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=173)
Countries and setting	Conducted in USA; Setting: Multicentre study at 20 sites in the USA
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were children and adolescents ages 7-17 with DSM-IV defined ADHD (any subtype) and comorbid depressive or anxiety symptoms that met minimum severity criteria; for example Children's Depression Rating Scale-Revised total score of >36 or Multidimensional Anxiety Scale for Children total score at least 1 SD above age and gender norms.
Exclusion criteria	History of psychosis, bipolar disease or serious medical illness. Patients judged by the investigator to be at serious suicidal risk and patients with a history of drug or alcohol abuse or evidence of illicit drug use during drug screen at time of study entry were excluded.
Recruitment/selection of patients	Patients were recruited by advertisement and referral
Age, gender and ethnicity	Age - Range: 7-17. Gender (M:F): Male 70%, Female 30%. Ethnicity: 84.15% White, 15.85% other
Further population details	1. ADHD subtype: All/mixed subtypes (Hyperactive/impulsive 2%, Inattentive 20.7%, Combined 77.3%). 2.

Study	Kratochvil 2005³⁸⁹
	Age: Mixed (Children and adolescents). 3. At risk population: General population 4. Comorbidities: Mixed (Generalised anxiety 31.85%, Specific phobias 13.55, Separation anxiety 9.25%, OCD 6.3, Panic 1.2%, Agoraphobia 1.5%, Dysthymia 14.95%, Major depression 45.7%, Adjustment 1.9%, Seasonal 1.5%, Other (NOS) 18.25%). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear (score at least 1 SD above age and gender norms).
Indirectness of population	No indirectness
Interventions	(n=106) Intervention 1: CNS stimulants - Atomoxetine. At study entry participants were randomised to receive fluoxetine (20mg) or placebo, and atomoxetine was added to this after 3 weeks. Atomoxetine was initiated at 0.5mg/kg per day and increased at weekly intervals to 0.8 and 1.2mg/kg per day. Duration 5 weeks. Concurrent medication/care: Not stated (but psychotropic/other drugs effecting CNS excluded) Further details: 1. Dose: 2. Method of titration: (n=46) Intervention 2: CNS stimulants – Atomoxetine and Fluoxetine. At study entry participants were randomised to receive fluoxetine (20mg) or placebo, and atomoxetine was added to this after 3 weeks. Atomoxetine was initiated at 0.5mg/kg per day and increased at weekly intervals to 0.8 and 1.2mg/kg per day. Duration 5 weeks. Concurrent medication/care: Not stated (but psychotropic/other drugs effecting CNS excluded) Further details: 1. Dose: 2. Method of titration:
Funding	Principal author funded by industry (Grants from Eli Lilly, GlaxoSmithKline, Cephalon and McNeil)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE and FLUOXETINE versus ATOMOXETINE</p> <p>- Actual outcome: ADHD-RS Change Score (total scores) at 5 weeks; Group 1: mean -24 (SD 13.6); n=106; Group 2: mean -20.5 (SD12.9) (n=37) Risk of bias: high; Indirectness of outcome: No indirectness</p> <p>Actual outcome: ADHD-RS Change Score (hyperactivity subscale) at 5 weeks; Group 1: mean -11.1 (SD 7.2); n=106, Group 2 mean: -9.9(6.8), n=37) Risk of bias: high; Indirectness of outcome: No indirectness</p> <p>Actual outcome: ADHD-RS Change Score (inattention subscale) at 5 weeks; Group 1: mean -12.9 (SD 7.5); n=106, Group 2 mean: -10.7(7.1) n=37 Risk of bias: high; Indirectness of outcome: No indirectness</p> <p>Actual outcome: drop out due to adverse events at 5 weeks; Group 1 3/127; Group 2 1/37</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Kratochvil 2011 ³⁹⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=101)
Countries and setting	Conducted in USA; Setting: 3 academic research sites
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Pea-body Picture Vocabulary Test-III A SS score of 70+ (2) attending day-care/pre-school 2 or more half days per week (3) living with the same guardian for 6+ months.
Exclusion criteria	(1) Concurrent psychotropic or other medications that have CNS effects (2) any current atomoxetine treatment (3) a current diagnosis of adjustment disorder, autism, psychosis, bipolar or suicidality (4) history of abuse (5) failure to respond to a trial of atomoxetine.
Recruitment/selection of patients	From October 2005 to June 2008. Other details not specified
Age, gender and ethnicity	Age - Range: 5 to 6 years. Gender (M:F): 63:30. Ethnicity: 86% White, (19% Hispanic or Latino), 11% Black or African American, 3% American Indian
Further population details	1. ADHD subtype: All/mixed subtypes (82% combined). 2. Age: Pre-schoolers (<6 years) (5-6 years old). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Mixed (Mixed (35% ODD)). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: 1st line (drug naive) (82% drug naive. Effective or ineffective treatment with atomoxetine was an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear (Mean total ADHD-RS scores were 38 (parent) and 36 (teacher)).
Extra comments	ADHD
Indirectness of population	Serious indirectness: 18% of participants not drug naive
Interventions	(n=51) Intervention 1: CNS stimulants - Atomoxetine. Single daily oral dose, but divided doses were permitted if necessary. 4 weekly and 1 biweekly visits allowed for flexible titration to 0.8, 1.2, 1.4 and a maximum 1.8 mg/kg per day, on the basis of tolerability and clinical judgement of the pharmacotherapist. Mean final daily dose was 1.4 mg/kg (+/-0.4). Duration 8 weeks. Concurrent medication/care: Not stated (but psychotropic/other drugs effecting CNS excluded) Further details: 1. Dose: 2. Method of titration: (n=50) Intervention 2: No treatment - Placebo. Single daily oral dose, but divided doses were permitted if

Study	Kratochvil 2011³⁹⁰
	necessary. 4 weekly and 1 biweekly visits allowed for flexible titration to 0.8, 1.2, 1.4 and a maximum 1.8 mg/kg per day, on the basis of tolerability and clinical judgement of the pharmacotherapist. Mean final daily dose was 1.5 mg/kg (+/-0.3). Duration 8 weeks. Concurrent medication/care: Not stated (but psychotropic/other drugs effecting CNS excluded) Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding (NIMH (and also Eli Lilly and some universities))
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome: ADHD-RS Parent Change Score at 8 weeks; Group 1: mean -13.2 (SD 1.7); n=44, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS Teacher Change Score at 8 weeks; Group 1: mean -12.5 (SD 1.7); n=44, Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: CGI stated as an outcome but not reported at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS Parent Change Score (hyperactivity subscale) at 8 weeks; Group 1: mean -6.2 (SD 1); n=44, Group 2: mean -2.8 (SD 0.8); n=49; Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS Parent Change Score (inattentive subscale) at 8 weeks; Group 1: mean -7.3 (SD 0.8); n=44, Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS Teacher Change Score (inattentive subscale) at 8 weeks; Group 1: mean -6.6 (SD 1); n=44, Risk of bias: high; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS Teacher Change Score (hyperactivity subscale) at 8 weeks; Group 1: mean -5.5 (SD 1); n=44, Risk of bias: high; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome: Drop out due to adverse events at 8 weeks; Risk of bias: high; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: high risk of attrition bias

Study	Kuperman 2001³⁹²
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Study	Kuperman 2001 ³⁹²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A standard clinical assessment conducted by a study physician consisting of a psychiatric evaluation utilising a structured diagnostic interview and medical history
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had to meet the following criteria: 1) the presence of full DSM-IV criteria for a diagnosis of ADHD at the time of study entry; 2) the presence of a chronic course of ADHD symptoms from childhood to adulthood; and 3) endorsement of moderate or severe level of impairment attributed to the ADHD symptoms.
Exclusion criteria	Any clinically significant chronic medical conditions, another current Axis 1 diagnosis, a history of tic disorders, mental retardation (IQ<80), organic brain disorders, any patient with recent seizure disorder, patients with eating disorders, patients taking any other psychotropic medication, females of child bearing age not using adequate contraception.
Recruitment/selection of patients	Patients were recruited from the community through the use of newspaper advertisements
Age, gender and ethnicity	Age - Mean (SD): Bupropion SR: 33.2 (10.8), Methylphenidate: 31.4 (7.3), Placebo: 32.2 (9.8). Gender (M:F): 21:9. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (A standard clinical assessment conducted by a study physician consisting of a psychiatric evaluation utilising a structured diagnostic interview and medical history). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Unclear line of therapy
Interventions	(n=11) Intervention 1: Bupropion . Sustained release bupropion was used and given at 8am and 4pm, while a placebo tablet was given at noon. Bupropion SR was titrated over 2 weeks to a maximum daily dose of 300mg/d, administered as 200mg at 8am and 100mg at 4pm. Duration 7 weeks. Concurrent medication/care: Subjects were not permitted to use any other psychotropic medications Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=8) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations).

Study	Kuperman 2001 ³⁹²
	<p>Methylphenidate was titrated over 1 week to a maximum dose of 0.9 mg/kg/d and divided into 3 doses, administered at 8am, noon, and 4pm. Duration 7 weeks. Concurrent medication/care: Patients were not permitted to use psychotropic medication during the study. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=11) Intervention 3: No treatment - Placebo. Placebo patients were given placebo doses at 8am, noon and 4pm. Duration 7 weeks. Concurrent medication/care: Patients were not permitted to use other psychotropic medication during the study. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Funded by Glaxo Wellcome)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Adult: Treatment response at 7 weeks; Group 1: 7/11, Group 2: 4/8; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: ADHD-RS at 7 weeks; Group 1: mean -13.7 (SD 6.9); n=11, Group 2: mean -10.1 (SD 8.3); n=8; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinued due to adverse events at 7 weeks; Group 1: 0/11, Group 2: 2/8; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BUPROPION versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Adult: Treatment response at 7 weeks; Group 1: 7/11, Group 2: 3/11; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: ADHD-RS at 7 weeks; Group 1: mean -13.7 (SD 6.9); n=11, Group 2: mean -12.4 (SD 10.6); n=11; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p>	

Study	Kuperman 2001 ³⁹²
<p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinued due to adverse events at 7 weeks; Group 1: 0/11, Group 2: 1/11; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Adult: Treatment response at 7 weeks; Group 1: 4/8, Group 2: 3/11; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: ADHD-RS at 7 weeks; Group 1: mean -10.1 (SD 8.3); n=8, Group 2: mean -12.4 (SD 10.6); n=11; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinued due to adverse events at 7 weeks; Group 1: 2/8, Group 2: 1/11; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study	Lee 2014 ⁴⁰⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in Japan, South Korea, Taiwan; Setting: 45 study sites: 10 in Korea, 29 in Japan and 6 in Taiwan
Line of therapy	Mixed line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Conners Adult ADHD Diagnostic Interview for DSM-IV

Study	Lee 2014 ⁴⁰⁰
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were required to meet additional criteria, which included a score of 2 or more on 6 or more items of either the inattentive or hyperactive/impulsive subscale scores at visits 1 and 2 on the Conners' Adult ADHD Rating Scale-Investigator-rated: Screening Version; and a CGI-ADHD-S score of 4 or more at visits 1 and 2.
Exclusion criteria	A history of bipolar disorder or schizophrenia, depressive disorder with 12 or more on the 17 item Hamilton Depression Rating Scale and current anxiety disorders.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 33.3 (8.8). Gender (M:F): 28:45. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Inattentive (39.7%). Hyperactive/impulsive (4.1%), Combined (56.2%)). 2. Age: Adults 18-65 years (Mean (SD): 33.3 (8.8)). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (Conners Adult ADHD Diagnostic Interview for DSM-IV). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear (2 or more on 6 or more items of either the inattentive or hyperactive/impulsive subscale scores, CGI-ADHD-S score of 4 or more).
Indirectness of population	Serious indirectness: 19.2% not stimulant naive
Interventions	<p>(n=37) Intervention 1: CNS stimulants - Atomoxetine. Treatment was initiated at the lowest dose (atomoxetine 40mg once daily) for the first two weeks, and during the 10 week treatment period, the dose was up titrated in a stepwise fashion (80 mg and 105 mg) to a maximum of 120 mg once daily if there were no issues with tolerability. Duration 10 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=37) Intervention 2: No treatment - Placebo. Placebo tablets were given once daily. Duration 10 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Funded by Eli Lilly and Company)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
<p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Adult: AAQoL at 10 weeks; Group 1: mean 19.6 (SD 17.8); n=36, Risk of bias: High; Indirectness of outcome: No indirectness</p>	

Study	Lee 2014 ⁴⁰⁰
Protocol outcome 2: ADHD symptoms at <3- or >6-months	<ul style="list-style-type: none"> - Actual outcome for Adult: Treatment response (CGI-ADHD-S) at 10 weeks; Group 1: 18/36, Group 2: 10/37; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS Total score at 10 weeks; Group 1: mean -18.9 (SD 11.1); n=36, Group 2: mean -9 (SD 8.8); n=37; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS Inattention subscale at 10 weeks; Group 1: mean -10 (SD 5.5); n=36, Group 2: mean -4.2 (SD 4); n=37; CAARS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS Hyperactivity subscale at 10 weeks; Group 1: mean -8.9 (SD 6.4); n=36, Group 2: mean -4.9 (SD 5.5); n=37; CAARS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months	<ul style="list-style-type: none"> - Actual outcome for Adult: Discontinuation due to adverse effects at 10 weeks; Group 1: 0/36, Group 2: 1/37; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study	Martenyi 2010 ⁴²⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=105)
Countries and setting	Conducted in Russia; Setting: 8 university clinics/hospitals
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Children
Subgroup analysis within study	Not stratified but pre-specified: Age (6-12 years vs 13-16 years)
Inclusion criteria	(1) 4+ on CGI-ADHD-S (2) minimum score of 25 (boys) and 22 (girls) on ADHD-S-IV Parent version (or more than 12 for their subtype) (3) included if washout completed/ stimulant naive.
Exclusion criteria	(1) weight less than 20kg, more than 60kg (2) experiencing no clinical benefit after adequate trial of

Study	Martenyi 2010 ⁴²⁹
	methylphenidate or amphetamine (3) history of bipolar, psychosis or pervasive developmental disorder (4) DSM-IV criteria for anxiety disorder (5) history of seizure disorders (6) taking anticonvulsant drugs (7) suicidal risk (8) serious medical illnesses (9) pregnant or breast feeding
Recruitment/selection of patients	Outpatients. Recruited from August 2004 to February 2005
Age, gender and ethnicity	Age - Range: 6 to 16 years. Gender (M:F): 90 male, 15 female. Ethnicity: All Caucasian
Further population details	1. ADHD subtype: All/mixed subtypes (72.4% combined, 24% inattentive, 5% hyperactive). 2. Age: Mixed (6-16 years (however, separate data for 6-12 years and 13-16 years reported)). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Not applicable / Not stated / Unclear (Many comorbidities excluded; no other details provided). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: 1st line (drug naive) (All stimulant naive; minority of participants had previously received medication used to treat ADHD (>13%)). 7. Severity: Not applicable / Not stated / Unclear (Mean total ADHD-RS-IV scores (parent) = 37.5).
Extra comments	. 6 - 12 years subgroup analysis
Indirectness of population	Serious indirectness: All participants were stimulant naive, however a minority (unclear however at least 13% had previously received medication specified on the review protocol: N=8 antipsychotics; N=3 tricyclic antidepressants; N=2 carbamazepine; "and some other centrally acting psychotropic drugs in individual cases").
Interventions	(n=72) Intervention 1: CNS stimulants - Atomoxetine. Screening and washout of at least 3 days. Single daily morning dose. Titration: 0.8mg/kg per day for 4 days, 1.2mg/kg per day for the remainder of the visit interval. From visit 5 (week not clarified) this could be decreased or increased depending on tolerability and improvement. Maximum dose of 1.8mg/kg per day. The mean final dose was 53mg/day (SD 22.8). The 6 week phase was followed by a 7-18 day period of drug discontinuation. Duration 6 weeks. Concurrent medication/care: All stimulant naive. Only drugs necessary for the patient's wellbeing were allowed. Use of antipsychotics or other CNS activity drugs were prohibited. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=33) Intervention 2: No treatment - Placebo. Identically matched placebo treatment. The 6 week phase was followed by a 7-18 day period of drug discontinuation. Duration 6 weeks. Concurrent medication/care: All stimulant naive. Only drugs necessary for the patient's wellbeing were allowed. Use of antipsychotics or other CNS activity drugs were prohibited. Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Company)

Study	Martenyi 2010 ⁴²⁹
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Treatment response at 6 weeks; Group 1: 52/72, Group 2: 16/33; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners' Parent Rating Scale (Revised, short form): oppositional subscale (adjusted for baseline score) at 6 weeks; Group 1: mean -1.3 (SD 3.4); n=72, Group 2: mean -0.6 (SD 3.45); n=33; CPRS ? Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-Parent:Inv hyperactivity/impulsive subscale (adjusted for baseline score) at 6 weeks; Group 1: mean -7.6 (SD 4.24); n=72, Group 2: mean -4.8 (SD 4.02); n=33; ADHD-RS hyperactivity/impulsive subscale 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-Parent:Inv inattentive subscale (adjusted for baseline score) at 6 weeks; Group 1: mean -8.7 (SD 4.24); n=72, Group 2: mean -6.5 (SD 4.6); n=33; ADHD-RS inattentive subscale 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Serious adverse events at All</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Serious adverse events (including deaths or suicidal ideation) at 6 weeks; Group 1: 0/72, Group 2: 0/33; Risk of bias: Low; Indirectness of outcome: No indirectness <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 6 weeks; Group 1: 1/72, Group 2: 0/33; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	NCT00246220;CR002479 trial: Medori 2008 ⁴⁴⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=401)
Countries and setting	Conducted in Germany; Setting: study conducted at 51 investigator sites in 13 European countries from April 2005 to June 2006
Line of therapy	Unclear

Study	NCT00246220;CR002479 trial: Medori 2008⁴⁴⁵
Duration of study	Intervention time: 5 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adult:
Subgroup analysis within study	Not applicable
Inclusion criteria	men and woman with a diagnosis of ADHD with diagnosis of ADHD according to the criteria of the Diagnostics and Statistical Manual of Mental diseases, Fourth Edition (DSM-IV) and confirmed by the Conners Adult ADHD symptoms from childhood following CAADID interview. CAARS total score of >24 at screening
Exclusion criteria	Patients were excluded if the investigator judged they (or their child) had a history of poor response or intolerance to methylphenidate; they had been diagnosed with any current clinically unstable psychiatric condition (e.g. bipolar disorder acute mood disorder) by the investigator, or they had been diagnosed with substance use disorder according to DSM-IV criteria within the last 6 months. Other exclusions included family history of psychosis , serious illnesses, hyperthyroidism, myocardial infarction, or stroke within 6 months of screening and history of seizures, glaucoma or uncontrolled hypertension
Recruitment/selection of patients	patients that met inclusion criterial between the time period April 2005 to June 2006
Age, gender and ethnicity	Age - Range: 18-65 years, Mean=34.0 years. Gender (M:F): 182/219. Ethnicity: 97.5% Caucasian (white), 2.5% other
Further population details	1. ADHD subtype: All/mixed subtypes (70.8% combined, 24.2% inattentive, 4% hyperactive-impulsive, 1% not specified). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Not applicable / Not stated / Unclear (non-responders to MPH were excluded from study). 7. Severity:
Extra comments	Mixed ADHD subtype: 70.8% combined, 24.2% inattentive, 4% hyperactive-impulsive, 1% not specified. Comorbidities included active or previous mood disorders reported by 48% of the study population and anxiety disorders reported by 30% of the population. Active or previous alcohol/substance abuse was reported by 0.7% and 13.5% subjects.
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Patients receiving 18 mg or 36 mg methylphenidate received the treatment dose for 5 weeks. Mean daily dose. 24mg/kg per day. Duration 5 weeks. Concurrent medication/care: Trial included a washout period of up to 4 weeks during which current therapy was tapered to discontinuation patients on a stable dosage of antidepressant therapy for at least 3 months prior to screening were allowed to continue at the same daily dose during the study with the exception of monoamine oxidase inhibitors which were tapered to discontinuation with a minimum washout period of 2 weeks

Study	NCT00246220;CR002479 trial: Medori 2008 ⁴⁴⁵
	<p>Further details: 1. Dose: 2. Method of titration:</p> <p>(n=96) Intervention 2: No treatment - Placebo. Patients were randomised into one of four treatment groups to receive oral doses of 18 mg, 36 mg or 72 mg placebo once daily. Patients receiving 18 mg or 36 mg placebo received the treatment dose for 5 weeks. Duration 5 weeks. Concurrent medication/care: Trial included a washout period of up to 4 weeks during which current therapy was tapered to discontinuation. Patients on a stable dosage of antidepressant therapy for at least 3 months prior to screening were allowed to continue at the same daily dose during the study with the exception of monoamine oxidase inhibitors which were tapered to discontinuation with a minimum washout period of 2 weeks Further details: 1. Dose: 2. Method of titration:</p> <p>(n=102) Intervention 3: CNS stimulants - Methylphenidate (including modified-release preparations). Patients in the 72 mg methylphenidate arm were titrated from a starting dose of 36 mg/day for 4 days to 54 mg/day for 3 days, after which 72 mg /day was delivered for 4 weeks. Mean daily dose of .96mg/kg per day. Duration 5 weeks. Concurrent medication/care: Trial included a washout period of up to 4 weeks during which current therapy was tapered to discontinuation patients on a stable dosage of antidepressant therapy for at least 3 months prior to screening were allowed to continue at the same daily dose during the study with the exception of monoamine oxidase inhibitors which were tapered to discontinuation with a minimum washout period of 2 weeks Further details: 1. Dose: 2. Method of titration:</p> <p>(n=102) Intervention 4: CNS stimulants - Methylphenidate (including modified-release preparations) . Patients receiving 18 mg or 36 mg methylphenidate received the treatment dose for 5 weeks. Mean daily dose .5mg/kg per day. Duration 5 weeks. Concurrent medication/care: Trial included a washout period of up to 4 weeks during which current therapy was tapered to discontinuation patients on a stable dosage of antidepressant therapy for at least 3 months prior to screening were allowed to continue at the same daily dose during the study with the exception of monoamine oxidase inhibitors which were tapered to discontinuation with a minimum washout period of 2 weeks Further details: 1. Dose: 2. Method of titration:</p> <p>(n=305) Intervention 5: CNS stimulants - Methylphenidate (including modified-release preparations) . OROS MPH combined. Duration 5 weeks. Concurrent medication/care: Trial included a washout period of up to 4 weeks during which current therapy was tapered to discontinuation patients on a stable dosage of antidepressant therapy for at least 3 months prior to screening were allowed to continue at the same daily dose during the study with the exception of monoamine oxidase inhibitors which were tapered to discontinuation with a minimum washout period of 2 weeks Further details: 1. Dose: 2. Method of titration:</p>

Study	NCT00246220;CR002479 trial: Medori 2008⁴⁴⁵
Funding	Study funded by industry (Janssen Pharmaceutica)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 36MG (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: CAARS Self Form Total Scores (mean change scores) at 5 weeks; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: CGI-S at 5 weeks; CGI-S 7 point scale Top=; Mean change in placebo group= -0.5(n=93) .MC in 18 mg/day methylphenidate group=-0.9(N=97).MC in 36 mg/day methylphenidate group=-0.90 (N=100)and MC in 72 mg/day methylphenidate group=-1.2 (n=98); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: CAARS Observer Form - Total (mean change scores) at 5 weeks; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing: missing:</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome: Drop out due to adverse events at 5 weeks; Group 1: 2/101, Group 2: 0/96 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing:</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE 36MG (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus METHYLPHENIDATE 72MG (INCLUDING MODIFIED-RELEASE PREPARATIONS)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: CAARS Self Form Total Scores (mean change scores) at 5 weeks;</p>	

Study	NCT00246220;CR002479 trial: Medori 2008 ⁴⁴⁵
	<p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome: CAARS Observer Form - Total (mean change scores) at 5 weeks;</p> <p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <p>- Actual outcome: Drop out due to adverse events at 5 weeks;</p> <p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing:</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS MPH COMBINED versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <p>- Actual outcome: CAARS Self Form Total Scores CAARS:S-S at 5 weeks; Group 1: mean -12.1 (SD 10.5); n=306, Group 2: mean -8 (SD 10); n=96</p> <p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing:</p> <p>- Actual outcome: CAARS Self Form Total Scores CAARS :0-SV at 5 weeks; Group 1: mean -12 (SD 13.7); n=306, Group 2: mean -5.8 (SD 11.3); n=96</p> <p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: currently active and stable psychiatric comorbidities in the study population included mood and anxiety disorders in 12% of patients and personality disorders in 1% of patients; Group 1 Number missing: ; Group 2 Number missing:</p>
<p>Protocol outcomes not reported by the study</p>	<p>Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months</p>

Study	Merged with Newcorn 2005 trial: Michelson 2001 ⁴⁵¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=297)
Countries and setting	Conducted in USA; Setting: 13 outpatient investigative sites
Line of therapy	Unclear
Duration of study	Intervention + follow up: 13 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Diagnosis confirmed by KSADS-PL (2) ADHD-RS score 1.5 standard deviations above age and gender norms
Exclusion criteria	(1) Patients who met diagnostic criteria for current major depression or anxiety disorder or for current or past bipolar or psychotic disorders (2) IQ below 80 (3) history of seizure disorder
Recruitment/selection of patients	Recruitment by referral and advertisements
Age, gender and ethnicity	Age - Range: 8 to 18 years. Gender (M:F): 178:102 (study 1) and 170:86. Ethnicity: 75.8% white, 17.9% African-American, 1% Asian, 2% Hispanic, 3% not specified
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed (38% ODD). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear (1.5 SDs above age and gender norms on ADHD RS).
Extra comments	Most patients met criteria for combined subtype of ADHD (proportion of subtype is stated for each treatment group in both studies)
Indirectness of population	No indirectness
Interventions	(n=213) Intervention 1: CNS stimulants - Atomoxetine. 12 to 18 day evaluation and medication washout period was followed by randomisation to dosage, for approximately 8 weeks. All patients began on 0.5 mg/kg per day, and this was titrated up to 0.8mg/kg and then 1.2 mg/kg at weekly intervals. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Moderate 2. Method of titration: Titrated to optimum dose (n=84) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:

Study	Merged with Newcorn 2005 trial: Michelson 2001 ⁴⁵¹
Funding	Study funded by industry (research funded by Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: Quality of life at <3- or >6-months - Actual outcome for Children (up to 18 years): Child Health Questionnaire psychosocial summary score at 8 weeks; Group 1: mean 6 (SD 9); n=84, Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-S at 8 weeks; Group 1: mean 4.8 (SD 0.9); n=84, Group 2: mean 4.7 (SD 0.8); n=84; 1-7 CGI-S Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS total at 8 weeks; Group 1: mean 13.6 (SD 14); n=84, Group 2: mean -5.8 (SD 10.9); n=83; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS inattention subscale at 8 weeks; Group 1: mean -7 (SD 8.1); n=84, Group 2: mean -2.5 (SD 6.6); n=83; ADHD-RS inattention subscale 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS hyperactivity impulsivity subscale at 8 weeks; Group 1: mean -6.6 (SD 7.1); n=84, Group 2: mean -3.2 (SD 5.6); n=83; ADHD hyperactivity impulsivity subscale 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R ADHD index at 8 weeks; Group 1: mean -8.9 (SD 9.7); n=84, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R hyperactive subscale at 8 weeks; Group 1: mean -4.1 (SD 4.9); n=84, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS-R cognitive subscale not extracted at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): CPRS-R oppositional subscale at 8 weeks; Group 1: mean -2.4 (SD 3.9); n=84, Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinued due to adverse events at 8 weeks; Group 1: 2/84, Group 2: 0/84; Risk of bias: High; Indirectness of outcome: No indirectness</p>	

Study	Merged with Newcorn 2005 trial: Michelson 2001⁴⁵¹
Protocol outcomes not reported by the study	Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: high risk of attrition bias

Study	Michelson 2002⁴⁴⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=170)
Countries and setting	Conducted in USA; Setting: 9 outpatient sites in the US
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) confirmed diagnosis by K-SADS-PL (2) 1.5 SDs above age and gender norms as assessed by ADHD-RS-IV
Exclusion criteria	(1) serious medical illness (2) history of psychosis or bipolar disorder (3) alcohol or drug abuse within the past 3 months (4) ongoing use of psychoactive medications other than the study drug
Recruitment/selection of patients	Recruited by referral or advertisements
Age, gender and ethnicity	Age - Range: 6 to 16 years. Gender (M:F): 120:50. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes (57.6% combined, 40.6% inattentive, 1.8% hyperactive impulsive). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed (20% ODD). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (55.3% had previous stimulant treatment). 7. Severity: Not applicable / Not stated / Unclear (1.5SDs above age and gender norms).
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	(n=85) Intervention 1: CNS stimulants - Atomoxetine. Single daily dose in the morning. Patients began on 0.5mg/kg per day for 3 days, followed by 0.75mg/kg per day for the remainder of the first week. The daily dose was then increased to 1mg/kg per day. Depending on response this could be increased to 1.5mg/kg per day. Duration 6 weeks. Concurrent medication/care: Not specified

Study	Michelson 2002⁴⁴⁹
	Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose (n=85) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): 25% reduction in ADHD-RS scores at 6 weeks; Group 1: 50/84, Group 2: 26/83; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS inattention subscale at 6 weeks; Group 1: mean -7.1 (SD 6.9); n=84, Group 2: mean -2.9 (SD 5.7); n=83; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS hyperactive impulsive subscale at 6 weeks; Group 1: mean -5.7 (SD 6.8); n=84, Group 2: mean -2.1 (SD 5.7); n=83; Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 6 weeks; Group 1: 2/85, Group 2: 1/85; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1 (ADHD symptoms): high risk of attrition bias Protocol outcome 2 (discontinuation): low risk of bias

Study	Michelson 2003⁴⁴⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=515)
Countries and setting	Conducted in USA; Setting: Two studies, the first at 14 sites, the second at 17 sites
Line of therapy	Mixed line

Study	Michelson 2003 ⁴⁴⁸
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Meet DSM-IV criteria at interview (CAAR-D) with moderate disability, confirmed by informant
Exclusion criteria	Comorbid psychiatric disorder. Episodic recreational drug use allowed, but not active use during the trial.
Recruitment/selection of patients	From clinics and advertisements
Age, gender and ethnicity	Age - Mean (SD): 40.2 (11.7). Gender (M:F): 144/102. Ethnicity: Not stated
Further population details	1. ADHD subtype: All/mixed subtypes (356 combined, 167 inattentive, 13 hyperactive/impulsive). 2. Age: Adults 18-65 years) (18-30y). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear (Nil). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Moderate (moderate and above).
Indirectness of population	No indirectness
Interventions	(n=270) Intervention 1: CNS stimulants - Atomoxetine. Atomoxetine, flexible dose 30-60mg twice a day. Duration 8 weeks. Concurrent medication/care: Nil Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=266) Intervention 2: No treatment - Placebo. Identical regimen to active treatment. Duration 8 weeks. Concurrent medication/care: nil Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Company)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: CAARS-INV, study 1 at 8 weeks; Group 1: mean -6 (SD 9.3); n=133, Group 2: mean -9.5 (SD 10.1); n=134

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27.6%; Group 2 Number missing: 23%

- Actual outcome for Adult: CAARS-INV, study 2 at 8 weeks; Group 1: mean -6.7 (SD 9.3); n=124, Group 2: mean -10.5 (SD 10.9); n=124

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 36%; Group 2 Number missing: 25%

Study	Michelson 2003 ⁴⁴⁸
	<p>- Actual outcome for Adult: CAARS-INV inattentive subscale, study 1 at 8 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27.6%; Group 2 Number missing: 23%</p> <p>- Actual outcome for Adult: CAARS-INV hyperactive/impulsive subscale, study 1 at 8 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27.6%; Group 2 Number missing: 23%</p> <p>- Actual outcome for Adult: CAARS-INV hyperactive/impulsive subscale, study 2 at 8 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 36%; Group 2 Number missing: 25%</p> <p>- Actual outcome for Adult: CAARS-INV inattentive subscale, study 2 at 8 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 36%; Group 2 Number missing: 25%</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <p>- Actual outcome for Adult: Drop out due to adverse events at 8 weeks; Group 1: 11/141, Group 2: 6/139 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27.6%; Group 2 Number missing: 23%</p> <p>- Actual outcome for Adult: Drop out due to adverse events (study 2) at 8 weeks; Group 1: 12/129, Group 2: 3/127 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 36%; Group 2 Number missing: 25%</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Mohammadi 2010 ⁴⁵⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Iran; Setting: Outpatient clinic and adolescent clinic at Roozbeh Psychiatric Hospital in Tehran, Iran
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks

Study	Mohammadi 2010 ⁴⁵⁶
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years): Children between ages of 6-14 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Total and/or subscale scores on ADHD-RS-IV School version of at least 1.5 standard deviations above norms for patient's age and gender.
Exclusion criteria	(1) History or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders or any current psychiatric comorbidity that required pharmacotherapy (2) evidence of suicide risk and intellectual disability
Recruitment/selection of patients	From the outpatient child and adolescent clinic at Roozbeh Psychiatric Hospital
Age, gender and ethnicity	Age – Range: 6-14 years old. Gender (M:F): 70% male/30% female. Ethnicity: Not specified
Further population details	1. ADHD subtype: Combined (100%). 2. Age: Children (6-12 years) (Children aged 6-14 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Not applicable / Not stated / Unclear (Many comorbidities excluded (psychiatric and significant chronic medical disorders). No further information). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: Not applicable / Not stated / Unclear (Not clearly stated, although all participants stated to be newly diagnosed and response to previous medication was not an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear (ADHD-RS-IV >1.5SD above general population. Mean ADHD-RS-IV subscales at baseline = ~15 (inattentive; parent) and 17 (hyperactivity/impulsivity; parent)).
Extra comments	Comorbid conditions: not stated.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: CNS stimulants – Methylphenidate (including modified-release preparations) .20-30 mg/day. 10mg/day during week 1, 20mg/day during week 2 and 30mg/day during week 3 if >30kg Duration 6 weeks. Concurrent medication/care: not stated Further details: 1. Dose: Not applicable / Not stated / Unclear (20-30mg/day depending on weight). 2. Method of titration: Fixed dose (Methylphenidate was titrated up during the trial according to a fixed schedule) (n=20) Intervention 2: Drugs used to treat Parkinson's disease – Amantadine. 100-150 mg/day depending on weight (100mg/day for <30kg and 150 mg/day for >30kg). Amantidine was titrated up during the trial according to a fixed schedule; 50 mg/day for week 1, 100mg/day for week 2 (one capsule in the morning and one at midday), and 150mg/day for week 3 (one capsule in the morning, one at midday, and one at 4pm). . Duration 6 weeks. Concurrent medication/care: Not described. Further details: 1. Dose: Not applicable / Not stated / Unclear (100-150mg/day depending on weight). 2.

Study	Mohammadi 2010⁴⁵⁶
	Method of titration: Fixed dose (Amantidine was titrated up during the trial according to a fixed schedule; 50 mg/day for week 1, 100mg/day for week 2, and 150mg/day for week 3).
Funding	Academic or government funding (Grant from Tehran University of Medical Sciences)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMANTADINE versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS (parent); inattentive subscale at 6 weeks; Group 1: mean 8.85 (SD 8.11); n=19, Group 2: mean 8.45 (SD 5.85); n=19; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS (teacher); inattentive subscale at 6 weeks; Group 1: mean 8.8 (SD 5.19); n=19, Group 2: mean 8.6 (SD 3.01); n=19; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS (parent); hyperactivity/impulsivity subscale at 6 weeks; Group 1: mean 9.4 (SD 6.75); n=19, Group 2: mean 8.8 (SD 5.65); n=19; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS (teacher); hyperactivity/impulsivity subscale at 6 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: low risk of bias

Study	Mohammadi 2012⁴⁵⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in Iran; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV

Study	Mohammadi 2012 ⁴⁵⁵
Stratum	Children (up to 18 years): Children
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) ADHD-RS-IV score of at least 1.5 standard deviations above norms for patient's age and gender
Exclusion criteria	(1) History or current diagnosis of pervasive developmental disorders, schizophrenia, or other psychiatric disorders (2) any current psychiatric comorbidity that required pharmacotherapy (3) any evidence of suicide risk or intellectual disability (4) any chronic medical condition including organic brain disorder, seizures, and current abuse of dependence on drugs the last 6 months. (5) hypertension or hypotension
Recruitment/selection of patients	Recruited from Roozbeh Psychiatric hospital
Age, gender and ethnicity	Age– Range: 6 to 14 years. Gender (M:F): 25:15. Ethnicity: not specified
Further population details	1. ADHD subtype: Combined (All patients had combined subtype of ADHD). 2. Age: Children (6-12 years) (Children 6-14 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Not applicable / Not stated / Unclear (Most comorbidities excluded, no details reported). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: 1st line (drug naïve) (First line). 7. Severity: Not applicable / Not stated / Unclear (Not reported).
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Methylphenidate tablets 20-30 mg doses depending on weight (20 mg/day for patients <30 kg, and 30 mg/day for patients over 30 kg. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear (20-30 mg/day). 2. Method of titration: Fixed dose (Fixed dose dependent on weight). (n=23) Intervention 2: No treatment - Standard treatment. Buspirone tablets 20-30 mg doses depending on weight (20 mg/day for patients less than 30 kg, and 30 mg/day for patients over 30 kg. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear (20-30 mg/day). 2. Method of titration: Fixed dose (Fixed dependent on weight).
Funding	Academic or government funding (Tehran University of Medical Sciences)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH GROUP versus BUSPIRONE	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV total (parent) at 6 weeks; Group 1: mean -15.6 (SD 7.81); n=20, Group 2: mean -8.95 (SD 8.73); n=20; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness	

Study	Mohammadi 2012⁴⁵⁵
	- Actual outcome for Children (up to 18 years): ADHD-RS-IV total teacher at 6 weeks; Group 1: mean -22.4 (SD 9.9); n=20, Group 2: mean -9.8 (SD 7.06); n=20; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study	Montoya 2009⁴⁵⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=151)
Countries and setting	Conducted in Spain; Setting: 12 specialised outpatient settings in Spain
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR and K-SADS-PL (for confirmation)
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Newly diagnosed (time since diagnosis ≤ 3 months) (2) treatment-naïve, with ADHD defined according to DSM-IV-TR (3) ADHDRS-IV-Parent:Inv total score ≥ 1.5 standard deviations above the age norm for their diagnostic subtype.
Exclusion criteria	(1) History of bipolar disorder, psychosis, pervasive developmental disorder or seizure disorder, glaucoma or hypertension (2) IQ below 70 (3) substance abuse in past 3 months (4) planned start of structured psychotherapy (5) taking regular psychoactive or sympathomimetic medication
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 6-15 years. Gender (M:F): 120 males, 31 females. Ethnicity: 96% Caucasian, 3.3% Hispanic, 0.7% African
Further population details	1. ADHD subtype: All/mixed subtypes (63.1% combined, 32.9% inattentive, 4% hyperactive). 2. Age: Mixed (Children and young people aged 6-15 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Mixed (46% of participants had any comorbidity (25.5% ODD; 16.8% tic

Study	Montoya 2009⁴⁵⁹
	disorder; 3.4% affective disorder; 12.8% anxiety disorder)). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: 1st line (drug naïve) (All participants were treatment naïve). 7. Severity: Not applicable / Not stated / Unclear (Mean total ADHD-RD-IV score (parent) = 39).
Extra comments	Comorbid conditions: 45.6% (type not stated). Subgroup analysis of subtypes and comorbidities available
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: CNS stimulants - Atomoxetine. Starting dose 0.5mg/kg per day during the first 2 weeks. Titrated to target dose of 1.2 mg/kg/day for the remaining 10 weeks. Because the medication was formulated in capsules, only discrete dosing was possible. Patients divided into 6 weight ranges to approximate target doses, and the target dose range was 0.4 to 0.9mg/kg per day for the 0.5mg/kg dose, and 0.8 to 1.4mg/kg per day for the 1.2mg/kg target dose. Duration 12 weeks. Concurrent medication/care: Treatment-naïve Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (Titrated to target dose). (n=51) Intervention 2: No treatment - Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: Treatment naïve Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Lilly Research Laboratories, Alcobendas, Spain)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv scale total at 12 weeks; Group 1: mean 26.3 (SD 12.7); n=100, Group 2: mean 34.8 (SD 12.3); n=51; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children 'up to 18 years): Conners' Parent Rating Scale (Revised, short form) total scores at 12 weeks; Group 1: mean 37.8 (SD 18.7); n=100, Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children 'up to 18 years): Conners' Parent Rating Scale (Revised, short form) hyperactivity subscale at 12 weeks; Group 1: mean 6.5 (SD 4.9); n=100, Group 2: mean 8.6 (SD 5.5); n=51; CPRS revised short form ? Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children 'up to 18 years): Conners' Parent Rating Scale (Revised, short form) oppositional subscale at 12 weeks; Group 1: mean 6.3 (SD 5.1); n=100, Group 2: mean 7.2 (SD 6.1); n=51; CPRS revised short form ? Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children 'up to 18 years): Conners' Parent Rating Scale (Revised, short form) cognitive problems subscale at 12 weeks; Group 1:

Study	Montoya 2009 ⁴⁵⁹
	mean 10.2 (SD 5.2); n=100, Group 2: mean 13.4 (SD 4.2); n=51; CPRS revised short form ? Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv inattention subscale at 12 weeks; Group 1: mean 14.5 (SD 6.5); n=100, Group 2: mean 19.6 (SD 5.9); n=51; ADHD RS IV 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv hyperactivity-impulsivity subscale at 12 weeks; Group 1: mean 11.9 (SD 7.3); n=100, Group 2: mean 15.2 (SD 7.7); n=51; ADHD RS IV 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Nagaraj 2006 ⁴⁶⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in India; Setting: Paediatric Neurodevelopment Clinic of the department of Paediatrics at the Advanced Paediatric Centre of the Postgraduate Institute of Medical Education and Research, Chandigarh, India
Line of therapy	Unclear
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children diagnosed with autism according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria.
Exclusion criteria	(1) Severe intellectual disability (2) any significant co-existing disease or illness (neurologic, cardiovascular, respiratory, genetic) (3) severe malnutrition (weight for age <60% of National Center for Health Statistics median)
Recruitment/selection of patients	Children were referred to the outpatient clinics of the centre with varying symptoms, including hyperactivity,

Study	Nagaraj 2006⁴⁶⁸
	aggression, stereotypes and language difficulties
Age, gender and ethnicity	Age – Other: Up to 12 years old. Gender (M:F): 34/5. Ethnicity: Not specified Check
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Children (6-12 years) 3. At risk population: 4. Comorbidities: ASD 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: 20% have had previous treatment
Interventions	(n=20) Intervention 1: Antipsychotics – Risperidone. 0.5mg daily for the first two weeks and then 1mg daily for the subsequent period. Further details: 1. Dose: 2. Method of titration: Fixed dose (n=20) Intervention 2: No treatment – Placebo. Placebo. Duration 6 months. Concurrent medication/care: No medication was given concurrently Further details: 1. Dose: 2. Method of titration:
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISPERIDONE versus PLACEBO	
Protocol outcome 1: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Children’s Global Assessment Score at 6 months; Group 1: mean 40.94 (SD 7.83); n=19, Group 2: mean 35.2 (SD 9.38); n=20; Global Assessment Scale 1-100 Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Nair 2009⁴⁷⁰
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India; Setting: semi-urban tertiary care hospital in Pondicherry, South India

Study	Nair 2009 ⁴⁷⁰
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Post-hoc subgroup analysis: Separate results presented for participants with comorbid conduct disorder, and for participants with comorbid ODD
Inclusion criteria	Children aged 4-12 years diagnosed with ADHD as per the DSM-IV criteria.
Exclusion criteria	(1) Children with history of sensitivity to drug testing (possibly those with previous intolerance excluded?) (2) Children suffering from organic disorders.
Recruitment/selection of patients	Children presenting at a tertiary hospital over a 2-year period. Children whose parents could not afford to pay for psychostimulant medication were invited to participate in the trial
Age, gender and ethnicity	Age - Mean (SD): 7.1 (2.5) range=4- 12 years. Gender (M:F): 4:1. Ethnicity: 100% Indian
Further population details	1. ADHD subtype: All/mixed subtypes (Combined (55%), others not stated). 2. Age: Mixed (4-12 years). 3. At risk population: General population (General population, possibly low SES group (children whose parents could not afford psychostimulant medication)). 4. Comorbidities: Mixed (15% conduct disorder, 12.5% seizures, 10% ODD). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear (Not stated. Likely first line, as parents of children included were unable to afford typical first line medication). 7. Severity: Not applicable / Not stated / Unclear (Total scores Vanderbilt rating scale 419 approx. 45).
Extra comments	The predominant subtype of ADHD was the combined type (55%). 15% of the study group also had conduct disorder, 12.5% had seizures, and 10% had ODD.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Clonidine. 8 µg/kg dose. Duration 4 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration: (n=25) Intervention 2: Mood stabilisers – Carbamazepine. No dosage details provided. Duration 4 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding

Study	Nair 2009 ⁴⁷⁰
Protocol outcome 1: ADHD symptoms at <3- or >6-months	<ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Vanderbilt ADHD rating scale (children with comorbid conduct disorder; number experiencing >25% improvement in symptoms): ODD group at 4 weeks; Group 1: 0/0, Group 2: 1/4; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Vanderbilt ADHD rating scale (children with comorbid conduct disorder; number experiencing >25% improvement in symptoms): Inattention group at 4 weeks; Group 1: 3/9, Group 2: 2/13; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Vanderbilt ADHD rating scale (children with comorbid conduct disorder; number experiencing >25% improvement in symptoms): Hyperactivity group at 4 weeks; Group 1: 18/21, Group 2: 3/19; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Vanderbilt ADHD rating scale (children with comorbid conduct disorder; number experiencing >25% improvement in symptoms): Impulsivity group at 4 weeks; Group 1: 15/18, Group 2: 4/17; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Vanderbilt ADHD rating scale (children with comorbid conduct disorder; number experiencing >25% improvement in symptoms): Conduct disorder group at 4 weeks; Group 1: 2/3, Group 2: 0/3; Risk of bias: Very high; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Very high risk of attrition bias

Study	Newcorn 2008 ⁴⁷⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=191)
Countries and setting	Conducted in USA; Setting: 20 sites in the USA
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical history and semi-structured interview
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects who met DSM-IV criteria for ADHD, ADHD symptoms was required to be at least 1.5 SD above the

Study	Newcorn 2008 ⁴⁷⁵
	Us age and gender norms as assessed by ADHD-RS-IV.
Exclusion criteria	Patients who had seizures, bipolar disorder, a psychotic illness, or a pervasive developmental disorder or who were taking concomitant psychoactive medications were excluded from the study.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 6-16. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Details unclear). 2. Age: Mixed (6-16). 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: ODD 5. Diagnostic method: DSM 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=82) Intervention 1: CNS stimulants - Atomoxetine. 0.8-1.8 mg/kg per day, administered as a divided twice daily dose. Duration 6 weeks. Concurrent medication/care: No concomitant psychoactive medication was permitted Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=82) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). 18-54 mg /day, administered as a single morning dose. Duration 6 weeks. Concurrent medication/care: No concomitant psychoactive medication was permitted Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=27) Intervention 3: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: No concomitant medication was permitted Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Supported by Eli Lilly and Company)

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

Protocol outcome 1: Quality of life at <3- or >6-months

- Actual outcome for Children (up to 18 years): CHQ at 6 Weeks; Group 1: mean 9.9 (SD 11.5); n=72, Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS Inattentive subscale at 6 Weeks; Group 1: mean -9.7 (SD 7.1); n=82, Group 2: mean -11 (SD

Study	Newcorn 2008 ⁴⁷⁵
	<p>7.2); n=82; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS Hyperactive subscale at 6 Weeks; Group 1: mean -8.2 (SD 7.2); n=82, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS Inattentive subscale at 6 Weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS at 6 Weeks; Group 1: mean -10.9 (SD 9.2); n=78, Risk of bias: High; Indirectness of outcome: No indirectness <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: Quality of life at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): CHQ at 6 Weeks; Group 1: mean 9.9 (SD 11.5); n=72, Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS Inattentive subscale at 6 Weeks; Group 1: mean -9.7 (SD 7.1); n=82, Group 2: mean -5.4 (SD 7.4); n=27; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS Hyperactive subscale at 6 Weeks; Group 1: mean -8.2 (SD 7.2); n=82, Group 2: mean -3.8 (SD 5.5); n=27; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS at 6 Weeks; Group 1: mean -10.9 (SD 9.2); n=78, Risk of bias: High; Indirectness of outcome: No indirectness <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE versus PLACEBO</p> <p>Protocol outcome 1: Quality of life at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): CHQ at 6 Weeks; Group 1: mean 9.8 (SD 11.8); n=75, Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS Inattentive subscale at 6 Weeks; Group 1: mean -11 (SD 7.2); n=82, Group 2: mean -5.2 (SD 7.4); n=27; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS Hyperactive subscale at 6 Weeks; Group 1: mean -8.2 (SD 7.2); n=82, Group 2: mean -3.8 (SD 5.5); n=27; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CPRS at 6 Weeks; Group 1: mean -13.5 (SD 8.2); n=76, Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the	CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All;

Study	Newcorn 2008⁴⁷⁵
study	Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Very high risk of bias

Study (subsidiary papers)	Newcorn 2013⁴⁷⁸ (Stein 2015⁵⁹⁸)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=340)
Countries and setting	Conducted in Multiple countries, USA; Setting: Conducted in 47 sites in the USA and Canada between November 2009 and September 2010.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 8 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD-RS-IV baseline score of 28 or more, and a CGI-S score of 4 or more.
Exclusion criteria	(1) Any controlled or uncontrolled psychiatric diagnosis (except oppositional defiant disorder) (2) risk of suicidality (3) history or presence of cardiac abnormalities or a primary sleep disorder (4) body weight of less than 55 lbs or a body mass index over the 95th percentile (6) use of another investigational product within 30 days of baseline (7) predominantly inattentive subtype of ADHD
Recruitment/selection of patients	440 outpatient subjects were screened and 340 were randomised. No other details provided.
Age, gender and ethnicity	Age - Range: 6-12 years. Gender (M:F): Define. Ethnicity: predominantly white (57.1), African American (36.1), Asian (0.6%), American Indian (0.3%), other (5.93%)
Further population details	1. ADHD subtype: All/mixed subtypes (Predominantly inattentive subtype was an exclusion criteria). 2. Age: Children (6-12 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear (Not stated). 7. Severity: Mixed (Possibly excluding mild?).
Extra comments	Predominantly hyperactive –impulsive= 1.83%, Combined subtype=96.1%, Predominantly inattentive =2.1% (this was an exclusion criteria- however 7 subjects with predominantly inattentive subtype were inadvertently

Study (subsidiary papers)	Newcorn 2013 ⁴⁷⁸ (Stein 2015 ⁵⁹⁸)
	randomised to treatment groups. These remained in the full set analysis when considering the intent to treat analyses.
Indirectness of population	No indirectness
Interventions	<p>(n=113) Intervention 1: Guanfacine. Guanfacine (GXR) was administered in the morning, on awakening and matching placebo in the evening at approximately 7 pm (+- 1.5 hours). Guanfacine (GXR) was administered in the morning, on awakening and matching placebo in the evening. The study consisted of a 5-week dose optimisation (days 1-35), a 3 week dose maintenance period (days 35-56) and a 9 day dose taper period. During dose optimisation a starting dose of 1 mg/d was titrated upward in 1 mg increments after a minimum of 1 week at the previous dose, based on clinical response and tolerability up to a maximum of 4 mg/d. Subjects were maintained on their optimal dose for 3 weeks (dose maintenance) during which efficacy and safety was assessed weekly and the dose could not be increased. A single 1 mg dose reduction was allowed during either dose optimisation or maintenance based on tolerability. After study completion subjects had their dose of drug tapered in 1 mg increments over a period of 9 days .The final efficacy evaluation was scheduled at visit 10. Duration 8 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=114) Intervention 2: Guanfacine. Placebo was administered in the morning, on awakening and matching Guanfacine (GXR) in the evening at approximately 7 pm (+-1.5 hours). The study consisted of a 5 week dose optimisation (days 1-35), a 3 week dose maintenance period (days 35-56) and a 9 day dose taper period. During dose optimisation a starting dose of 1 mg/d was titrated upward in 1 mg increments after a minimum of 1 week at the previous dose, based on clinical response and tolerability up to a maximum of 4 mg/d. Subjects were maintained on their optimal dose for 3 weeks (dose maintenance) during which efficacy and safety was assessed weekly and the dose could not be increased. A single 1 mg dose reduction was allowed during either dose optimisation or maintenance based on tolerability. After study completion subjects had their dose of drug tapered in 1 mg increments over a period of 9 days .The final efficacy evaluation was scheduled at visit 10. Duration 8 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=113) Intervention 3: No treatment - Placebo. Placebo (AM) and Placebo (PM). Duration 8 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=227) Intervention 4: Guanfacine. AM and PM combined data. Duration 8 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p>

Study (subsidiary papers)	Newcorn 2013⁴⁷⁸ (Stein 2015⁵⁹⁸)
Funding	Study funded by industry (Clinical research and writing/editorial support was funded by the sponsor, Shire Development LLC)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE ALL ACTIVE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Investigator administered ADHD-RS-IV total scores at 8 weeks (visit 10); Group 1: mean -20 (SD 12.97); n=221, Group 2: mean -11 (SD 12.93); n=112; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Investigator administered ADHD-RS-IV hyperactivity/impulsivity subscale at 8 weeks (visit 10); Group 1: mean -10 (SD 6.77); n=215, Group 2: mean -5.3 (SD 6.71); n=112; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Investigator administered ADHD-RS-IV inattention subscale at 8 weeks (visit 10); Group 1: mean -9.9 (SD 7.12); n=215, Group 2: mean -5.7 (SD 7.01); n=112; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Academic outcomes (literacy and numeracy) at <3- or >6-months - Actual outcome for Children (up to 18 years): Weiss Functional Impairment Rating Scale - Academic Performance (Least square mean ANCOVA) at 8 weeks (visit 10); Mean -0.34 (95%CI -0.54 to -0.13); Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study (subsidiary papers)	Palumbo 2008⁴⁹⁰ (Daviss 2008¹⁹⁹, Cannon 2009¹³⁶)
Study type	RCT
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in USA; Setting: University of Rochester Clinical Trials Co-ordination Center (CTCC). Four sites participated: University of Cincinnati, University of Rochester, University of Pittsburgh and State University of New York Buffalo.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 16 weeks

Study (subsidiary papers)	Palumbo 2008⁴⁹⁰ (Daviss 2008¹⁹⁹, Cannon 2009¹³⁶)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 7-12 years of any race/ethnic background and in school were enrolled. Each subject met DSM-IV criteria for ADHD of any sub-type. A designated teacher in daily contact with the subject had to indicate the presence of sufficient number of ADHD symptoms using the DSM-IV and rate the severity of these symptoms on the Iopa Conners Rating Scale. A designated parent daily contact with the subject had to indicate the presence of sufficient number of ADHD symptoms at home in Iopa Conners Rating Scale. Investigators rating of global function on CGAS had to be less than or equal to 70 with difficulty in at least two areas such as school and home.
Exclusion criteria	Subjects were excluded if there was evidence of a tic disorder, major depression, pervasive developmental disorder, autism, psychosis, mental retardation or other medical disorders that would preclude safe use of MPH or clonidine. Family history of long QT syndrome, cardiomyopathy or premature (less than 45 years) death were also exclusions
Recruitment/selection of patients	School officials were contacted regarding participation in the study according to institutional review board guidelines and adherence to specific school-based policies between October 2000 and April 2004
Age, gender and ethnicity	Age - Mean (SD): 9.5 (1.6). Gender (M:F): 98:24. Ethnicity: white= 78%, black=11%, Hispanic=6% and other=5%
Further population details	1. ADHD subtype: All/mixed subtypes (75% combined). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (45% ODD, 9% conduct disorder). 5. Diagnostic method: DSM (47% had received stimulants, 7% had received clonidine). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear (CGAS score of less than 70).
Extra comments	ADHD subtype data not provided for overall population. Breakdown for individual treatments groups provided. Majority of the subjects (~75% had combined type ADHD)
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Treatment period of 16 weeks which included 8 week dose titration period and 8 week dose maintenance period. In the titration period, MPH was administered as immediate-release MPH (5 mg capsule) or matching placebo tablets. Dosing was initiated with one capsule (5 mg) before school. After 3 days, adding an additional 5 mg capsule at lunchtime was allowed. These doses were adjusted to optimal effect based on regular reports provided by the teacher and parents. The daily dose was allowed to be increased by one 5 mg capsule every 3 school days. If ADHD symptoms were worse than the baseline state or were a problem later in the day, then a third 5 mg dose was added after school. These doses were administered at 7 am, 11

Study (subsidiary papers)	Palumbo 2008 ⁴⁹⁰ (Daviss 2008 ¹⁹⁹ , Cannon 2009 ¹³⁶)
	<p>am, and 3 pm. The dose titration was continued until either the optimal dose or the maximum dose of 60 mg/day was reached. During the 8 week titration period, subjects received MPH (or placebo) at the doses found to be optimal. Duration 16 weeks. Concurrent medication/care: Previous use of MPH or clonidine was permitted. However any treatment had to be discontinued at least 6 weeks (2 weeks for MPH) before enrolment. All psychosocial interventions were recorded at enrolment and did not allow any change in these treatments during the study Further details: 1. Dose: 2. Method of titration:</p> <p>(n=31) Intervention 2: Clonidine. Treatment period of 16 weeks which included 8 week dose titration period and 8 week dose maintenance period. In the titration period, Clonidine was administered as brand name Catapres (0.1 mg scored tablets) or matching scored placebo tablets. Dosing was initiated with 1/2 tablet at bedtime. The dose was increased by 1/2 tablet every 3 years initially using a 3 times daily dosing schedule (before school, after school, bedtime). A fourth dose (lunchtime) could be added if needed due to waning efficacy or to reduce side effects. The dose titration was continued until either the optimal dose or the maximum dose of 60 mg/day was reached. During the 8 week titration period, subjects received clonidine (or placebo) at the doses found to be optimal. Duration 16 weeks. Concurrent medication/care: Previous use of MPH or clonidine was permitted. However any treatment had to be discontinued at least 6 weeks (2 weeks for MPH) before enrolment. All psychosocial interventions were recorded at enrolment and did not allow any change in these treatments during the study by dividing the dose further. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=32) Intervention 3: Clonidine and methylphenidate combination. Treatment period of 16 weeks which included 8 week dose titration period and 8 week dose maintenance period. In the titration period, Clonidine was administered as brand name Catapres (0.1 mg scored tablets) or matching scored placebo tablets. Dosing was initiated with 1/2 tablet at bedtime. The dose was increased by 1/2 tablet initially using a 3 times daily dosing schedule (before school, after school, bedtime). A fourth dose (lunchtime) could be added if needed due to waning efficacy or to reduce side effects. The dose titration was continued until either the optimal dose or the maximum dose of 60 mg/day was reached. After 4 weeks, methylphenidate was then added and titrated up to the optimal dose throughout the following 4 weeks. Duration 16 weeks. Concurrent medication/care: Previous use of MPH or clonidine was permitted. However any treatment had to be discontinued at least 6 weeks (2 weeks for MPH) before enrolment. All psychosocial interventions were recorded at enrolment and did not allow any change in these treatments during the study by dividing the dose further. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=30) Intervention 4: No treatment - Placebo. Placebo tablets as administered for drugs. Duration 16 weeks. Concurrent medication/care: Previous use of MPH or clonidine was permitted. However any</p>

Study (subsidiary papers)	Palumbo 2008⁴⁹⁰ (Daviss 2008¹⁹⁹, Cannon 2009¹³⁶)
	treatment had to be discontinued at least 6 weeks (2 weeks for MPH) before enrolment. All psychosocial interventions were recorded at enrolment and did not allow any change in these treatments during the study by dividing the dose further. Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding (Project supported by NINDS grant 5R01 NS039087. Additional NIG support came from K23 MH065375 and K24 AA000301)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at 16 weeks; Conners ASQ-T mean difference adj for baseline; very high risk of bias. Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Behavioural outcomes at 16 weeks: CGAS mean difference adjusted for baseline; very high risk of bias. Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Drop out due to adverse events at 16 weeks: discontinuation due to adverse events; high risk of bias. Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at 16 weeks; Conners ASQ-T mean difference adj for baseline; very high risk of bias. Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Behavioural outcomes at 16 weeks: CGAS mean difference adjusted for baseline; very high risk of bias. Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Drop out due to adverse events at 16 weeks: discontinuation due to adverse events; high risk of bias. Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: COMBINATION versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at 16 weeks; Conners ASQ-T mean difference adj for baseline; very high risk of bias. Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Drop out due to adverse events at 16 weeks: discontinuation due to adverse events; high risk of bias. Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Paterson 1999 ⁴⁹³
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Australia; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV ADHD symptom checklist questionnaire
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects were eligible for inclusion if they reported the presence of at least four inattentive and/or five hyperactive symptoms during the previous 6 months.
Exclusion criteria	Subjects were excluded from the study on the grounds of either having an insufficient ADHD score, or comorbidity for other major psychiatric disorders including a history of current substance abuse. Patients were screened for organic disorders that would contraindicate the use of dexamphetamine. All patients had a sample of urine tested to screen for illicit substance abuse.
Recruitment/selection of patients	Two psychiatrists working in private practice, screened consecutive patients for a research trial into adult ADHD using a questionnaire based on the DSM-IV symptoms.
Age, gender and ethnicity	Age - Range: 19-57. Gender (M:F): 27:18. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Adults 18-65 years) (19-57). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV ADHD symptom checklist questionnaire). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Unclear line of therapy
Interventions	(n=24) Intervention 1: CNS stimulants - Dexamphetamine. Subjects began at a low dose and the dose was gradually increased, patients were told to take the dose before early afternoon to avoid insomnia. For the first week patients took one tablet each morning after breakfast. For the second week, they took one tablet after breakfast and one tablet after lunch. For the third week, they took two tablets after breakfast and one after lunch. For the remaining three weeks, patients were instructed that they could take up to six tablets per day but incremental increases were not to be more than one tablet per day, with two days between increases. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose

Study	Paterson 1999⁴⁹³
	(n=21) Intervention 2: No treatment - Placebo. Placebo tablets were given with identical instructions to dexamphetamine tablets. Duration 6 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Research grant from the Health Department of Western Australia)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMPHETAMINE versus PLACEBO	
Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Adult: CGI-I score of 1 or 2 at 6 weeks; Group 1: 14/24, Group 2: 0/21; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; ADHD symptoms at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study (subsidiary papers)	PATS trial: Greenhill 2006²⁹⁰ (Kollins 2006³⁷⁴)
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	2 (n=165)
Countries and setting	Conducted in USA; Setting: Six academic sites (Columbia University, Duke University, John Hopkins University, New York University, University of California, Irvine and University of California, Los Angeles.)
Line of therapy	1st line
Duration of study	Intervention time: 5 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 35-65 months, age and sex adjusted T score more than or equal to 65 on the Hyperactive-Impulsive

Study (subsidiary papers)	PATS trial: Greenhill 2006 ²⁹⁰ (Kollins 2006 ³⁷⁴)
	<p>subscale of both the Conners Parent and Teacher rating scales, score <55 on the Child Global Assessment scale, met DSM-IV criteria for ADHD, hyperactive/impulsive or combined subtype, on Parent Diagnostic Interview Schedule for Children-IV and clinical interview by experienced clinician; symptoms were required to be present for a minimum of 9 months, IQ > 70 as on the Differential Abilities scale; children scoring <70 were considered for inclusion if their composite score from the Vineland Adaptive Behaviour scale was >70, Participation in a school-type programme at least 2 half-days/week, where class included at least 8 same age peers; if child had been expelled from an eligible programme in the 3 months before screening, they could be considered for enrolment (these children were not required to have Teachers Conners scales for inclusion, but previous teacher rating were sought for baseline if there was no other teacher at that time), child must have been residing with primary caretaker for at least 6 months before screening, systolic and diastolic blood pressure below 95th percentile for age and gender. Pre-schoolers who continued to meet ADHD severity criteria after 10 weeks of parent training continued onto the open label phase.</p>
Exclusion criteria	<p>Children or their parents could not understand or follow instructions given in the study, if either of the following conditions were met: evidence of moderate to severe adverse events or evidence of a much improved response to any dose of MPH or another stimulant or >5 weeks of exposure to at least 30mg/day of MPH or equivalent doses of other stimulants. use of any other psychotropic medication or had taken an investigational drug in the past 30 days; episodic use of sympathomimetic decongestants for the common cold were allowed under the study physician's supervision, a history of motor or vocal tics or Tourette's syndrome, major medical conditions that would interfere with involvement in a long-term study or could be affected negatively by MPH, children were excluded if there were current evidence of adjustment disorder, autism, psychosis, significant suicidality or other psychiatric disorder in addition to ADHD that required treatment with additional medication. Evidence of current physical, sexual or emotional abuse, living with anyone who currently abuses stimulants or cocaine, history of bipolar in both biological parents</p>
Recruitment/selection of patients	<p>Patients were recruited from six academic sites from clinics, paid and public service advertisements in newspapers and on the radio, primary care physicians, nursery schools, day care centres and kindergartens. Study was comprised of seven stages. Pre-schoolers who were eligible to enter the controlled medication phases were those who continued meet ADHD severity criteria after 10 weeks of parent training. This involved an open label safety lead in phase. Children who tolerated all open MPH doses in the led-in phase then entered the 5 week crossover titration phase</p>
Age, gender and ethnicity	<p>Age - Range: 3-5.5 years. Gender (M:F): 122/43. Ethnicity: 63% white, 18% black, 18% hispanic, 18%, Asian 1%, Alaskan native 0.6%</p>
Further population details	<p>1. ADHD subtype: All/mixed subtypes (24% of the study population were of the hyperactive-impulsive subtype of ADHD and 76% were of the combined subtype of ADHD). 2. Age: Pre-schoolers (<6 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Mixed (Oppositional defiant disorder (52%), communication disorder (22%), elimination disorder (8%), specific phobia (8%), anxiety disorder (8%), developmental coordination disorder (3%), conduct disorder (2%), Pica (2%), Adjustment disorder</p>

Study (subsidiary papers)	PATS trial: Greenhill 2006²⁹⁰ (Kollins 2006³⁷⁴)
	(2%), reactive attachment disorder (2%), OCD (0.7%), sleepwalking disorder (0.3%)). 5. Diagnostic method: DSM (Diagnostic interview schedule for children IV- Parent version). 6. Line of treatment: 1st line (drug naive) (All participants were stimulant naive). 7. Severity: Not applicable / Not stated / Unclear
Extra comments	24% of the study population were of the hyperactive-impulsive subtype of ADHD and 76% were of the combined subtype of ADHD.55% of the study sample had ODD as a co-morbidity, 20% had communication disorder, 8% has elimination disorder, 7% specific phobia, 10% had anxiety disorder,4% had developmental co-ordination disorder,3% had conduct disorder, 0.6% had adjustment disorder and 0.6% had both obsessive-compulsive disorder and sleepwalking disorder
Indirectness of population	No indirectness
Interventions	<p>(n=165) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Subjects were randomised to one of five sequences of four different MPH doses (1.25, 2.5, 5, 7.5 mg) and placebo admixture t.i.d in identical capsules for 1 week each. Duration 5 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=165) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). Subjects were randomised to one of five sequences of four different MPH doses (1.25, 2.5, 5, 7.5 mg) and placebo administered t.i.d in identical capsules for 1 week each. Duration 5 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=165) Intervention 3: CNS stimulants - Methylphenidate (including modified-release preparations). Subjects were randomised to one of five sequences of four different MPH doses (1.25, 2.5, 5, 7.5 mg) and placebo administered t.i.d in identical capsules for 1 week each. Duration 5 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=142) Intervention 4: CNS stimulants - Methylphenidate (including modified-release preparations). Subjects were randomised to one of five sequences of four different MPH doses (1.25, 2.5, 5, 7.5 mg) and placebo administered t.i.d in identical capsules for 1 week each. Duration 5 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=165) Intervention 5: No treatment - Placebo. Subjects were randomised to one of five sequences of four different MPH doses (1.25, 2.5, 5, 7.5 mg) and placebo administered t.i.d in identical capsules for 1 week each. Duration 5 weeks. Concurrent medication/care: None reported</p>

Study (subsidiary papers)	PATS trial: Greenhill 2006²⁹⁰ (Kollins 2006³⁷⁴)
	Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding (National institute of Mental Health and various US universities)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): SNAP-IV total score (Parent-Teacher composite) at 5 weeks; Group 1: mean 1.46 (SD 0.57); n=61, Group 2: mean 17.79 (SD 0.61); n=53; SNAP-IV Unclear Top=Unclear Risk of bias: All domain - Very High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Children (up to 18 years): Excellent responders (as defined by SNAP-IV) at 5 weeks; Group 1: 7/61, Group 2: 13/53 Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 5 weeks; Group 1: 1/61, Group 2: 0/53 Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Pliszka 2000⁵⁰²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic Interview Schedule for Children

Study	Pliszka 2000 ⁵⁰²
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects had to meet DISC criteria for ADHD and not meet DISC criteria for major depression episode, manic episode, or tic disorder. In addition, the child could not have any history of psychosis or have signs of psychosis or significantly depressed mood on the mental status examination. The child had to be at least 1.5 SD above the mean for his/her age and sex on the IOWA CTRS I/O factor. The score on the parent Conners Global Index had to be similarly elevated. The KBIT composite IQ could not be lower than 75.
Exclusion criteria	Not specified
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 8.1(1.4). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=20) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . The starting doses for children weighing less than 60lb was 5mg; for children above 60lb it was 10mg. if there was improvement in all 3 ratings (morning, afternoon and evening), the child continued to receive one dose in the morning for week two. If there was no improvement on the afternoon teacher rating a noon dose was added for week 2. If there was no improvement in the parent evening ratings, an after-school dose was added. Duration 3 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=18) Intervention 2: No treatment - Placebo. Placebo subjects were randomly assigned to follow either the methylphenidate or Adderall algorithm. Duration 3 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Funded by Shire Richwood Inc)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI score ≤2 at 3 weeks; Group 1: 13/20, Group 2: 5/18; Risk of bias: High; Indirectness of outcome: No</p>	

Study	Pliszka 2000 ⁵⁰²
indirectness	Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 3 weeks; Group 1: 1/20, Group 2: 0/18; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; ADHD symptoms at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Low risk of bias

Study (subsidiary papers)	Reimherr 2007 ⁵²¹ (Robison 2010 ⁵²⁹)
Study type	RCT (Patient randomised; Crossover: not stated)
Number of studies (number of participants)	(n=47)
Countries and setting	Conducted in USA; Setting: Not stated
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) At least moderate ADHD symptoms and the UTAH criteria (2) Non-childbearing women
Exclusion criteria	(1) Depression, generalized anxiety disorder, PTSD, bipolar, schizophrenia or other psychotic disorders (2) Seizure disorders (3) hyperthyroidism and hypothyroidism
Recruitment/selection of patients	From August 2004 to December 2005 at the University of Utah
Age, gender and ethnicity	Age - Range: 18 to 65 years. Gender (M:F): 31:16 . Ethnicity: not stated
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not stated?). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated /

Study (subsidiary papers)	Reimherr 2007 ⁵²¹ (Robison 2010 ⁵²⁹)
	Unclear
Extra comments	38% had comorbid emotional dysregulation, 40% had comorbid emotional dysregulation and oppositional defiant disorder
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . Subjects started on 18mg a day and increased every 2 to 3 days by 9mg, depending on tolerance. This was up to a maximum dose of 90mg/day. Once a patient rated much improved or better on the CGI-I or improved 50% on the WRAADDS, the dose remained constant. Generally a stable dose was obtained in 2 weeks and held constant for the last 2 weeks. Duration 4 weeks. Concurrent medication/care: Not stated Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=47) Intervention 2: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding (McNeil Pediatrics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS total scores at 4 weeks; Group 1: mean 21.4 (SD 14.1); n=47, Group 2: mean 31.3 (SD 14.8); n=47; ADHD-RS 0-54 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; Indirectness of outcome: No indirectness ; Baseline details: ethnicity not stated; Group 1 Number missing: 1, Reason: reasons not stated. (6 also eliminated after randomization but before treatment, not stated why); Group 2 Number missing: 1, Reason: reasons not stated

- Actual outcome: ADHD-RS inattention subscale scores at 4 weeks; Group 1: mean 12 (SD 8.1); n=47, Group 2: mean 17.8 (SD 7.6); n=47; ADHD-RS inattention subscale 0-27 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; Indirectness of outcome: No indirectness ; Baseline details: ethnicity not stated; Group 1 Number missing: 1, Reason: reasons not stated. (6 also eliminated after randomization but before treatment, not stated why); Group 2 Number missing: 1, Reason: reasons not stated

- Actual outcome: ADHD-RS hyperactivity/impulsivity subscale scores at 4 weeks; Group 1: mean 9.5 (SD 6.7); n=47, Group 2: mean 14.1 (SD 7.4); n=47; ADHD-RS hyperactivity/impulsivity subscale 0-27 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; Indirectness of outcome: No indirectness ; Baseline details: ethnicity not stated; Group 1 Number missing: 1, Reason: reasons not stated. (6 also

Study (subsidiary papers)	Reimherr 2007 ⁵²¹ (Robison 2010 ⁵²⁹)
eliminated after randomization but before treatment, not stated why); Group 2 Number missing: 1, Reason: reasons not stated - Actual outcome: CGI-I Score of 1 or 2 at 4 weeks; Risk of bias: All domain - ; Indirectness of outcome: No indirectness - Actual outcome: WRAADDs emotional dysregulation subscale at 4 weeks; Group 1: mean 5.1 (SD 3.9); n=47, Group 2: mean 7.7 (SD 3.5); n=47 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Retz 2012 ⁵²³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=162)
Countries and setting	Conducted in Germany; Setting: Randomisation performed by Medice's Galenic Department.
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV and Wender Utah Rating scale
Stratum	Adult: Adults 18+years
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) undergone a washout period of at least 2 weeks for any psychopharmacological drug
Exclusion criteria	(1) subjects with a score of less than 30 on the Wender Utah Rating Scale (2) IQ of less than 85 (2) dementia, schizophrenia, bipolar disorder, current major depression, acute anxiety disorders and other unstable psychiatric conditions (3) any other serious medical conditions (4) subjects with drug or alcohol dependence during 6 months before screening (5) pregnant or nursing women (6) BMI of less than 20 or a body weight of 130kg or over (6) any other psychopharmacological drugs being taken
Recruitment/selection of patients	Block randomisation, recruitment not specified
Age, gender and ethnicity	Age - Range: 18+ years. Gender (M:F): 76:86. Ethnicity: Not specified
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not stated). 2. Age: Adults 18-65 years) (Mean age approx. 37 years). 3. At risk population: Not applicable / Not stated / Unclear (Not reported). 4.

Study	Retz 2012⁵²³
	Comorbidities: Not applicable / Not stated / Unclear (Most current comorbidities excluded. Unclear N of those not excluded.). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear). 7. Severity: Not applicable / Not stated / Unclear (CGI Severity = 5.2).
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	<p>(n=84) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). 2 week titration period followed by 6 weeks of continued dose. Medication was individually titrated BID after breakfast and lunch to an optimal dose on the basis of tolerability and according to the body weight with a maximum daily dose of 1mg/kg starting with 10-30mg/day. Patients were assigned to one of four weight classes (less than 55kg, 55-69kg, 70-104kg, 105-130kg) with doses of 40, 60, 80 and 120mg daily respectively. At week 8 the mean daily doses were 66+/- 20mg. Duration 8 weeks. Concurrent medication/care: Not specified. 29.8% had previously received methylphenidate treatment Further details: 1. Dose: 2. Method of titration:</p> <p>(n=78) Intervention 2: No treatment - Placebo. Placebo. At week 8 the mean daily doses were 78+/- 17mg. Duration 8 weeks. Concurrent medication/care: not specified. 37.2% had previously received methylphenidate treatment Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Medice, Germany)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (EXTENDED RELEASE) versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Adult: CGI score of 1 or 2 (% improved or very much improved) at 8 weeks; Group 1: 42/84, Group 2: 19/78; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Treatment response at 8 weeks; Group 1: 42/84, Group 2: 14/78; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Drop out due to adverse events at 8 weeks; Group 1: 3/84, Group 2: 1/78; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All;

Study	Retz 2012⁵²³
study	Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Riahi 2010⁵²⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Iran; Setting: Psychiatry clinic at Roozbeh Hospital in Tehran
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Wender Utah Criteria
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) psychotropic medications to be stopped 2 weeks prior to the study
Exclusion criteria	(1) major psychiatric or medical problems (e.g. mood and anxiety disorders)
Recruitment/selection of patients	From the Roozbeh hospital. 6 patients after randomisation rejected to use medication, so another block of 6 patients were added and randomly assigned to the study
Age, gender and ethnicity	Age - Range of means: 31.3(7.2), 32.1(7). Gender (M:F): 18:23. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Other antidepressants - Reboxetine. Started at 4mg in the morning and then increased to 8mg daily (4mg in the morning and 4mg in the afternoon). No further details. Duration 6 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose (n=17) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks. Concurrent medication/care: No

Study	Riahi 2010⁵²⁶
	<p>details</p> <p>Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (Tehran University of Medical Sciences)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REBOXETINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Conners Adult ADHD Rating Scale inattentiveness subscore at 6 weeks; Group 1: mean 11.31 (SD 5.17); n=22, Group 2: mean 16.05 (SD 4.65); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: Conners Adult ADHD Rating Scale hyperactivity subscore at 6 weeks; Group 1: mean 10.54 (SD 4.89); n=22, Group 2: mean 11.47 (SD 5.14); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: Conners Adult ADHD Rating Scale ADHD index subscore at 6 weeks; Group 1: mean 15.77 (SD 6.36); n=22, Group 2: mean 21.05 (SD 5.6); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: Conners Adult ADHD Rating Scale total score at 6 weeks; Group 1: mean 21.86 (SD 9.63); n=22, Group 2: mean 27.47 (SD 8.18); n=17; CAARS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Global Assessment of Functioning scale at 6 weeks; Group 1: mean 6.13 (SD 0.83); n=22, Group 2: mean 5.05 (SD 0.42); n=17; GAF ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Drop out due to adverse events at 6 weeks; Group 1: 2/23, Group 2: 1/17; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Rosler 2009⁵³² (Rosler 2010⁵³⁴)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=359)

Study (subsidiary papers)	Rosler 2009 ⁵³² (Rosler 2010 ⁵³⁴)
Countries and setting	Conducted in Germany; Setting: 28 study centres across Germany
Line of therapy	Mixed line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Study subjects fulfilled DSM-IV criteria for ADHD. Diagnosis was established by psychiatric expert assessment including a German version of the ADHD Rating Scale-IV
Exclusion criteria	Individuals with low intelligence (IQ<85), schizophrenia, bipolar disorder, acute depressive episode, acute anxiety disorders and other unstable psychiatric conditions were excluded, as were subjects with any serious medical illness. Subjects with evidence of drug/alcohol dependence during the preceding 6 months had participated in a previous drug trial in the last 30 days. Subjects treated with any psychopharmacological drug before study inclusion.
Recruitment/selection of patients	Subjects were outpatients. No other details reported
Age, gender and ethnicity	Age - Other: > 18 years. Gender (M:F): 178/179. Ethnicity: not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Proportion not reported). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: Mixed line (including drug naive) (38.3% of the study population had received earlier stimulant treatment). 7. Severity:
Extra comments	Breakdown of ADHD subtypes in participant not available for overall population.
Indirectness of population	No indirectness
Interventions	<p>(n=241) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). MPH ER is a MPH preparation with a proportion of 50% immediate release MPH and 50% of extended release MPH. Medication was titrated b.i.d after breakfast and lunch during the first 5 weeks to a maximum dose of 60 mg/day starting with 10 mg/day. The interval between the two doses should be of 6-8 hours. The minimum maintenance dose after week 5 was 20 mg/day. Duration 24 weeks. Concurrent medication/care: psychopharmacological drug in addition to study medication were not included Further details: 1. Dose: 2. Method of titration:</p> <p>(n=118) Intervention 2: No treatment - Placebo. Matching Placebo. Duration 24 weeks. Concurrent medication/care: psychopharmacological drug in addition to study medication were not included Further details: 1. Dose: 2. Method of titration:</p>

Study (subsidiary papers)	Rosler 2009⁵³² (Rosler 2010⁵³⁴)
Funding	Study funded by industry (Study funded by Medice)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH EXTENDED RELEASE (MPH ER) versus PLACEBO GROUP	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDs) at 24 Weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Very high

Study	Rugino 2003⁵³⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in USA; Setting: Not specified
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Reliable transportation to and from the development center; 2) regular school attendance; 3) an average Conners Teacher Rating Scale ADHD index t score of 70 or higher; 4) an average percentile score for the ADHD Rating Scale IV of 70 or higher; and 5) a verbal intelligence quotient of 80 or higher.
Exclusion criteria	1) Acute medical or uncontrolled psychiatric illness; 2) allergy to modafinil or any of the components of the tablet; 3) mitral valve prolapse, left ventricular hypertrophy, cardiac ischemia, clinically significant cardiac arrhythmia, or a history of syncope; 4) use of the following medications within 30 days before the study:

Study	Rugino 2003 ⁵³⁸
	psychoactive medications other than stimulants prescribed to manage ADHD, anti-epileptics, or medications metabolised primarily through the hepatic cytochrome P450 system; 5) more than three migraine headaches within 3 months before the study; 6) female with potential of becoming pregnant during the study; 7) uncontrolled seizure disorder; 8) sleep disorder with insomnia; and 9) history of manic episodes or psychosis
Recruitment/selection of patients	Patients that presented to the regional development centre were recruited
Age, gender and ethnicity	Age - Range: 5 to 15 years. Gender (M:F): 15:9. Ethnicity: 100% Caucasian
Further population details	1. ADHD subtype: All/mixed subtypes (16 combined type, 4 inattentive, 1 hyperactive impulsive). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed (6 ODD, 3 enuresis, 4 learning disorder, 2 adjustment disorder, 2 borderline intelligence quotient (both in the modafinil group), 1 selective mutism (in the placebo group)). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear (Above 70 on ADHD-RS-IV).
Extra comments	Study was terminated early due to primary investigator relocating to another state.
Indirectness of population	No indirectness
Interventions	<p>(n=11) Intervention 1: CNS stimulants - Modafinil. Mean dose of 264mg (+/- 50mg). Range 200mg - 300mg. If a patient developed a severe adverse event or acute illness the medication was immediately discontinued and the patient was withdrawn from the study. If the patient developed a potentially severe adverse event, or an adverse event, the medication dosage was reduced to the maximum tolerated dosage. If a minor adverse event occurred that required medical management for longer than 2 weeks, the dose was reduced to the maximum tolerated dose. Dosages were increased based on response, as judged by the Conners DSM-IV total t score. Once the dosage was stable for at least 5 days, the study was concluded for that patient. Duration 6 weeks (+/- 3.3 weeks). Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose</p> <p>(n=11) Intervention 2: No treatment - Placebo. Placebo. Duration 5.3 weeks (+/- 3.3 weeks). Concurrent medication/care: Not specified Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL versus PLACEBO	
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS total scores at 6 weeks (mean); Group 1: mean 14 (SD 6.7); n=11, Group 2: mean 14.7 (SD</p>	

Study	Rugino 2003 ⁵³⁸
	3.2); n=11; ADHD-RS-IV 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
	Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 6 weeks (mean); Group 1: 1/11, Group 2: 0/11; Risk of bias: Low; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Safavi 2016 ⁵³⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Iran; Setting: Conducted at a clinic of child psychiatry affiliated with the Shahrekord University of Medical Sciences.
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Being 3-6 years old, suffering from hyperactive/impulsive or mixed subtype of ADHD comorbid with DBDs diagnosed by a child psychiatrist based on DSM-V.
Exclusion criteria	Having mental retardation or other developmental disorders and any physical disorder, and being on treatment with any psychotropic drug during the last 4 weeks. Besides that, if children showed significant or intolerable adverse effects during the treatment, they were excluded from the study.
Recruitment/selection of patients	Study population selected based on convenience sampling from children referred to the clinic.
Age, gender and ethnicity	Age - Mean (SD): 4.495 (1.18). Gender (M:F): 33 male, 9 female. Ethnicity: Not stated.
Further population details	1. ADHD subtype: All/mixed subtypes (36 combined, 6 hyperactive/impulsive). 2. Age: Pre-schoolers (<6 years) (3-6 years old). 3. At risk population: Looked after children 4. Comorbidities: Not applicable / Not

Study	Safavi 2016⁵³⁹
	stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=21) Intervention 1: Antipsychotics - Risperidone. MPH and Risperidone. Risperidone was started with a single dose of 1.25 mg/day and was increased by 0.25 - 0.5 mg each week to a maximum dose of 2mg/day. . Duration 6 weeks. Concurrent medication/care: Both groups were taking methylphenidate. Methylphenidate was started at a dose of 2.5 mg twice daily and was increased 2.5-5mg each week based on the treatment response and the patients tolerance, to a maximum of 20/day. Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose</p> <p>(n=21) Intervention 2: No treatment - Standard treatment. MPH. Methylphenidate was started at a dose of 2.5 mg twice daily and was increased 2.5-5mg each week based on the treatment response and the patients tolerance, to a maximum of 20/day. Duration 6 weeks. Concurrent medication/care: Both groups were taking methylphenidate. Methylphenidate was started at a dose of 2.5 mg twice daily and was increased 2.5-5mg each week based on the treatment response and the patients tolerance, to a maximum of 20/day. Further details: 1. Dose: Mixed 2. Method of titration: Titrated to optimum dose</p>
Funding	Academic or government funding (This research was financially supported by the Research and Technology Deputy of the Shahrekord University of Medical Sciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RISPERIDONE versus STANDARD TREATMENT

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Children (up to 18 years): CGI-I scores reported by parents at 6 weeks PT; Group 1: 16/21, Group 2: 13/21

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD total score - Conners Parent Rating Scale (CPRS) at 6 weeks PT; Group 1: mean 30.52 (SD 15.81); n=21, Group 2: mean 33.85 (SD 15.22); n=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; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0

Study	Safavi 2016 ⁵³⁹
	<p>- Actual outcome for Children (up to 18 years): Hyperactivity - Conners Parent Rating Scale (CPRS) at 6 weeks PT; Group 1: mean 7.52 (SD 3.46); n=21, Group 2: mean 7.14 (SD 4.21); n=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; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0</p> <p>- Actual outcome for Children (up to 18 years): Inattention - Conners Parent Rating Scale (CPRS) at 6 weeks PT; Group 1: mean 6.67 (SD 3.79); n=21, Group 2: mean 6.67 (SD 3.98); n=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; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0</p> <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Oppositional defiant disorder - Conners Parent Rating Scale (CPRS) at 6 weeks PT; Group 1: mean 7.24 (SD 3.75); n=21, Group 2: mean 8.76 (SD 3.86); n=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; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0</p> <p>Protocol outcome 4: Serious adverse events at All - Actual outcome for Children (up to 18 years): Reported side effects by parents at 6 weeks PT; Group 1: 17/21, Group 2: 17/21 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0</p> <p>Protocol outcome 5: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Parents decided to discontinue medication at 6 weeks PT; Group 1: 5/21, Group 2: 0/21 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 2 - Discontinued before week 3 due to severely increased appetite and sleepiness. 3 - Discontinued due to decreased appetite, agitation and nervousness and aggression. Group 2 Number missing: 0</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-

Study	Safavi 2016⁵³⁹
	months

Study	Sallee 2009⁵⁴⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=324)
Countries and setting	Conducted in USA; Setting: 51 sites in the USA
Line of therapy	Unclear
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) minimum baseline score of 24 on ADHD-RS-IV
Exclusion criteria	(1) any current severe Axis 1 or Axis 2 disorders or any other current uncontrolled comorbid psychiatric diagnosis (excluding ODD) (2) weight less than 25kg (3) morbid obesity (4) current medication that affects blood pressure or heart rate (except for ADHD therapies, which were discontinued during the washout period) (5) hypertension or orthostatic hypotension (6) abnormal ECG or vital signs (7) previous treatment of ADHD with guanfacine, or intolerance to guanfacine
Recruitment/selection of patients	From March to October 2004
Age, gender and ethnicity	Age - Range: 6 to 17 years. Gender (M:F): 223: 89. Ethnicity: 67% white, 17% black, 9% Hispanic, 2.8% Asian or Pacific Islander, 0.3% Native American
Further population details	1. ADHD subtype: All/mixed subtypes (73% combined, 26% inattentive, 2% hyperactive/impulsive). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Mixed (5.6% ODD). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Mixed (Mean ADHD-RS-IV score of 40.1 (SD 8.65)).
Indirectness of population	No indirectness
Interventions	(n=258) Intervention 1: Guanfacine. Randomised to 1,2,3 or 4mg per day of guanfacine which was stratified by weight (less than 75 pounds, or 75 to 110 pounds). Dosage taken once daily in the morning. Duration 6 weeks (plus 3 weeks discontinuation). Concurrent medication/care: Not specified Further details: 1. Dose: Mixed 2. Method of titration: Fixed dose

Study	Sallee 2009⁵⁴⁵
	(n=66) Intervention 2: No treatment - Placebo. Placebo. Duration 6 weeks (plus 3 weeks discontinuation). Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:
Funding	Principal author funded by industry (Shire Development)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV total scores (adjusted) at 6 weeks; Group 1: mean -19.6 (SD 13.9); n=243, Group 2: mean -12.2 (SD 13); n=63; ADHD RS 0-54 Top=High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 25 - Actual outcome for Children (up to 18 years): Treatment response (CGI I score of 1 or 2) at 6 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 25</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 6 weeks; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 88; Group 2 Number missing: 25</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Scahill 2001⁵⁵²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in USA; Setting: The Tic Disorders Clinic of the Yale Child Study Center
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline	Adequate method of assessment/diagnosis: clinical evaluation by an interdisciplinary team consisting of a

Study	Scahill 2001 ⁵⁵²
condition	child psychiatrist, a child psychiatrist nurse specialist, and/or a psychologist
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects aged 7-15 year, a DSM-IV diagnosis of ADHD (any type), a DSM-IV tic disorder (any type), and a score of 1.5 or more standard deviation units for age and gender on the 10-item Conners hyperactivity index rated by the teacher or a parent. Children had to be enrolled in the same school for at least a month before entry, with no planned change in school placement for at least 10 weeks after entry
Exclusion criteria	Evidence of current major depression, generalised anxiety disorder, separation anxiety disorder, or psychotic symptoms (based on all available information); WISC-R IQ <70; and a prior adequate trial of guanfacine (dose of 1.5mg or more/day for at least 2 weeks) Subjects had to be free of all psychotropic medication for at least two weeks and free of any significant medical problem. Children with moderate or more severe tic symptoms (Yale Global Tic Severity Scale total tic core >22) or significant obsessive compulsive symptoms (Children's Yale-Brown Obsessive Compulsive Scale total; score >15) were also excluded
Recruitment/selection of patients	Subjects were recruited from the Tic Disorders Clinic of the Yale Child Study Center
Age, gender and ethnicity	Age - Range: 7-14. Gender (M:F): 31:3. Ethnicity: Caucasian (29), African-American (2), Hispanic (2), Asian (1)
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Mixed (7-14 years). 3. At risk population: General population 4. Comorbidities: Tic disorder and Tourette's (Tourette's disorder (20), Chronic motor tic disorder (12), Stimulant-induced tic disorder (2)). 5. Diagnostic method: DSM (clinical evaluation by an interdisciplinary team consisting of a child psychiatrist, a child psychiatrist nurse specialist, and/or a psychologist). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Very serious indirectness: 70% naive
Interventions	(n=17) Intervention 1: Guanfacine. At screening, parents were given a blister pack containing placebo capsules and instructed to give the capsules to their children three times a day, the placebo capsules were gradually replaced with guanfacine, beginning with a single 0.5mg dose at bedtime (the morning and afternoon doses remained placebo). On day 4, the morning dose of placebo was replaced with 0.5mg of guanfacine, and on day 8 the afternoon dose was replaced with guanfacine. Duration 8 weeks. Concurrent medication/care: Prior to entry parents were advised on how to taper their child's current ineffective medication Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=17) Intervention 2: No treatment - Placebo. Placebo capsules were given three times a day. Duration 8 weeks. Concurrent medication/care: Prior to entry parents were advised on how to taper their child's current

Study	Scahill 2001 ⁵⁵²
	ineffective medication Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Funded by grants from the Children's Clinical Research Center, Mental Health Research Centre and the Tourette Syndrome Association)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD Rating Scale Hyperactive/Impulsive subscale at 8 weeks; Group 1: mean 10.8 (SD 8.1); n=17, Group 2: mean 16.3 (SD 8.1); n=17; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CGI score of 1 or 2 at 8 weeks; Group 1: 9/17, Group 2: 0/17; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD Rating Scale Total score at 8 weeks; Group 1: mean 23.6 (SD 13.6); n=17, Group 2: mean 31.7 (SD 11.2); n=17; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD Rating Scale Inattention subscale at 8 weeks; Group 1: mean 12.8 (SD 7.2); n=17, Group 2: mean 15.4 (SD 5.4); n=17; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: Low risk of bias Protocol outcome 2: Low risk of bias

Study	Scahill 2015 ⁵⁵³
Study type	RCT (Site randomised; Parallel)
Number of studies (number of participants)	1 (n=62)
Countries and setting	Conducted in USA; Setting: Research units on the Paediatric Psychopharmacology Autism Network
Line of therapy	Mixed line

Study	Scahill 2015 ⁵⁵³
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Based on clinical assessment and corroborated by the Autism Diagnostic Observational Schedule and the Social Communication Questionnaire
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	A minimum score of 24 on the parent-rated Aberrant behaviour Checklist-hyperactivity subscale, a CGI-S score of moderate or greater and an IQ of 35 (or mental age of 18 months) or greater.
Exclusion criteria	Children with a significant medical condition by history, physical examination, or laboratory testing were excluded; females with a positive pregnancy test were also excluded. Children with a lifetime diagnosis of psychosis or bipolar disorder or current diagnosis of major depression, obsessive-compulsive disorder, or substance abuse were excluded.
Recruitment/selection of patients	Subjects recruited from clinic registries, current referrals to the active clinical programs at each site, local website announcements, and outreach to parent support groups.
Age, gender and ethnicity	Age - Range: 5-14. Gender (M:F): 53:9. Ethnicity: White 65%, Black 18%, Asian 8%, Pacific Islander 3%, Mixed 6%
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Children (6-12 years) (5-14 years). 3. At risk population: General population 4. Comorbidities: ASD (Primary diagnosis). 5. Diagnostic method: DSM (Based on clinical assessment and corroborated by the Autism Diagnostic Observational Schedule and the Social Communication Questionnaire). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=30) Intervention 1: Guanfacine. The starting dose was 1mg per day, children weighing less than 25kg remained on the 1mg dose until day 14, and if well-tolerated the dose could be increased to 2mg until day 28 and increased to 3mg for the remaining 3 weeks of the trial. Children weighing 25kg or more were eligible for an increase to 2mg at day 7, 3mg at day 17 and 4mg at day 21 or 28. Duration 8 weeks. Concurrent medication/care: Subjects were required to be medication free at baseline Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=32) Intervention 2: No treatment - Placebo. Placebo treatment not described. Duration 8 weeks. Concurrent medication/care: Subjects were required to be medication free at baseline Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>

Study	Scahill 2015 ⁵⁵³
Funding	Academic or government funding (Funded by NIMH grants)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE EXTENDED RELEASE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS at 8 weeks; Mean 25.2 (95%CI 21.44 to 29.03); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Treatment response at 8 weeks; Group 1: 15/30, Group 2: 3/32; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Aberrant Behaviour Checklist - hyperactivity subscale at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Serious adverse events at All - Actual outcome for Children (up to 18 years): Serious adverse events at 8 weeks; Group 1: 1/30, Group 2: 0/32; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinued due to adverse events at 8 weeks; Group 1: 4/30, Group 2: 0/32; Risk of bias: high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: high risk of attrition bias

Study	Simonoff 2013 ⁵⁷⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in United Kingdom; Setting: Department of Child and Adolescent Psychiatry, Kings College London, Institute of Psychiatry
Line of therapy	Unclear

Study	Simonoff 2013 ⁵⁷⁵
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Participant inclusion criteria was were 7-15 years of age, a diagnosis of ICD-10 Hyperkinetic disorder (HD) and full scale IQ of 3—69. Diagnosis of HD was through Child and Adolescent Psychiatric Assessment (CAPA). Symptoms of autism were measured with the parent reported Special Communication Questionnaire (SCQ) Additional criteria was living in a stable situation and regular school attendance
Exclusion criteria	Participant inclusion criteria was were 7-15 years of age, a diagnosis of ICD-10 Hyperkinetic disorder (HD) and full scale IQ of 3—69. Diagnosis of HD was through Child and Adolescent Psychiatric Assessment (CAPA). Symptoms of autism were measured with the parent reported Special Communication Questionnaire (SCQ) Additional criteria was living in a stable situation and regular school attendance
Recruitment/selection of patients	890 children (764 through community screening, 129 through clinical referral) for eligibility between June 005 and July 2008. Community screening involved using the up to date Special Education Needs Register in four health districts to identify eligible patients. Also individual special schools were also approached from recruitment areas.
Age, gender and ethnicity	Age - Mean (SD): 134 (28) in months. Gender (M:F): 85:37. Ethnicity: not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Mixed (7-15). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: ICD (ICD-10). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Severe
Extra comments	ADHD sub-type not reported
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Immediate release methylphenidate supplied as Equasym in 5, 10, and 20 mg tablets. Participants were assessed on three daily doses 0.5 (LOW DOSE), 1.0(MEDIUM DOSE), and 1.5 (HIGH DOSE) mg/kg, given in increasing dose and delivered 3 times daily at breakfast, lunchtime and after school. At the end of the titration, two senior medical investigators independently judged optimal dose for each participant using parent, teacher and clinician ratings on adverse events and behavioural improvement on the parent and teachers Connors ADHD index and hyperactivity scale. This dose was then prescribed for the remainder of the 16 week trial. Duration 16 weeks. Concurrent medication/care: not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose

Study	Simonoff 2013⁵⁷⁵
	(n=61) Intervention 2: No treatment - Placebo. a matching placebo in identical "doses" was manufactured. Duration 16 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Study was funded by The Health Foundation, formerly the PPP Foundation)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH GROUP versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Conners Parent ADHD Index at 16 weeks; Group 1: mean 19.1 (SD 10.93); n=61, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Teacher ADHD Index at 16 weeks; Group 1: mean 14.5 (SD 9.37); n=61, Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Teacher ADHD Index (Hyperactivity) at 16 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Conners Parent ADHD Index (Hyperactivity) at 16 weeks; Group 1: mean 7.7 (SD 5.47); n=61, Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 16 weeks; Group 1: 5/61, Group 2: 0/61; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1: High risk of bias Protocol outcome 2: Low risk of bias
Study	Singer 1995⁵⁷⁶
Study type	RCT (Patient randomised; Crossover: 1 week)

Study	Singer 1995 ⁵⁷⁶
Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in USA; Setting: Johns Hopkins Hospital (USA)
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children not receiving other medication. The diagnosis of TS and ASDHD were made by a paediatric neurologist using Diagnostic and Statistical Manual IIR criteria, with independent confirmation by a child psychologist.
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Range: 7.2-13.6 years. Gender (M:F): 31/3. Ethnicity: 33 Caucasian, 1 African American
Further population details	1. ADHD subtype: 2. Age: Children (6-12 years) (7.2-13.6). 3. At risk population: General population 4. Comorbidities: Tic disorder and Tourette's 5. Diagnostic method: DSM (DSM-III). 6. Line of treatment: 1st line (drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=34) Intervention 1: Tricyclic antidepressants - Amitriptyline. Dosage schedules were standardised within and between all treatment groups; each child started with one capsule per day (evening) and added one additional capsule every week to a maximum daily dose of one capsule four times a day. The patient then was maintained of the highest daily dose for an additional 2 weeks (total treatment time was 6 weeks). Each capsule contained a fixed amount of medication or placebo: for desipramine, 25mg. The total daily dose of desipramine mimicked the dosage successfully used by Donnelly et al to treat non-TS children with ADHD. Each patient was maintained at the highest dose that did not produce side effects. Duration 6 weeks. Concurrent medication/care: Patients were not receiving any other medication Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (Patients were maintained on the highest dose that did not produce side effects).</p> <p>(n=34) Intervention 2: Clonidine. Dosage schedules were standardised within and between all treatment groups; each child started with one capsule per day (evening) and added one additional capsule every week to a maximum daily dose of one capsule four times a day. The patient then was maintained of the highest daily dose for an additional 2 weeks (total treatment time was 6 weeks). Each capsule contained a fixed</p>

Study	Singer 1995⁵⁷⁶
	<p>amount of medication or placebo: for clonidine, 0.05mg. The total daily dose of clonidine, 0.2mg/d, prescribed as 0.05mg four times a day, was based on the successful treatment regimen reported by Hunt et al. Each patient was maintained at the highest dose that did not produce side effects. Duration 6 weeks. Concurrent medication/care: Patients were not receiving other medications. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (Each patient was maintained at the highest dose that did not produce side effects.).</p> <p>(n=34) Intervention 3: No treatment - Placebo. Each capsules contained a fixed amount of medication or placebo. Duration 6 weeks. Concurrent medication/care: Patients were not receiving other medication Further details: 1. Dose: 2. Method of titration:</p>
Funding	Academic or government funding (Tourette Syndrome Association and the United States Public Health Service)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DESIPRAMINE versus PLACEBO</p> <p>Protocol outcome 1: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Mother/Teacher CBCL - Hyperactivity subscale at 6 weeks; Group 1: mean 68.6 (SD 1.4); n=34, Group 2: mean 75.8 (SD 1); n=34; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus DESIPRAMINE</p> <p>Protocol outcome 1: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Mother/Teacher CBCL - Hyperactivity subscale at 6 weeks; Group 1: mean 70.7 (SD 1.2); n=34, Group 2: mean 68.6 (SD 1.4); n=34; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO</p> <p>Protocol outcome 1: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Mother/Teacher CBCL - Hyperactivity subscale at 6 weeks; Group 1: mean 70.7 (SD 1.2); n=34, Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Singer 1995⁵⁷⁶
Risk of bias details	Low risk of bias

Study	Spencer 1995⁵⁹²
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	(n=25)
Countries and setting	Conducted in USA; Setting: Not specified
Line of therapy	Mixed line
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-III
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD-III diagnosis of childhood onset and current ADHD
Exclusion criteria	(1)Excluded for having other psychiatric disorders only if treatment with MPH was contraindicated or compliance to the trial could be jeopardised (2) any clinically significant chronic medical conditions or abnormal baseline laboratory values (3) history of tics disorder, IQ of less than 75, organic brain disorders, clinically unstable psychiatric conditions, or substance or alcohol abuse or dependence within the 6 months preceding the study or currently used psychotropics
Recruitment/selection of patients	Massachusetts General Hospital, Boston
Age, gender and ethnicity	Age - Range: 18 to 60 years. Gender (M:F): Define. Ethnicity: All non-Hispanic
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Mixed (26% past major depression with severe impairment, 52% with at least moderate impairment, 35% current anxiety disorder). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . Participants were titrated up to 0.5mg/kg per day by week 1, 0.75mg/kg per day by week 2, and up to 1mg/kg per day by week 3, unless adverse effects emerged. Average dose of 0.92mg/kg per day by week 3(0.04 SD). Duration 3 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:

Study	Spencer 1995⁵⁹²
	(n=25) Intervention 2: No treatment - Placebo. Placebo. Duration 3 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Treatment response (CGI-I score of less than 2 and at least 30% reduction in individual rating scale scores) at 3 weeks; Group 1: 18/23, Group 2: 1/23 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 2</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Spencer 2002⁵⁹¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=291)
Countries and setting	Conducted in USA; Setting: 17 investigational sites in the USA
Line of therapy	Mixed line
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were required to have a score on the ADHD-RS at least 1.5 SDs above the age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total scores for the

Study	Spencer 2002 ⁵⁹¹
	combined subtype.
Exclusion criteria	Patients were excluded from the study if, based on their genotype, they were characterised as poor metabolisers of CYP2D6. They were also ineligible to participate if they weighed less than 25kg (55lb) at study entry; had a documented history of bipolar I or II disorder or any history of psychosis; had any organic brain disease or a history of any seizure disorder; were taking any psychotropic medication; had any history of alcohol or drug abuse within the past 3 months; or had significant prior or current medical conditions.
Recruitment/selection of patients	Patients were recruited by referral and by advertisement
Age, gender and ethnicity	Age - Mean (SD): Atomoxetine: 9.7 (1.6) Placebo: 10 (1.5). Gender (M:F): 201:52. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Atomoxetine: Inattentive 18.6%, Hyperactive 0.8%, Combined 80.6% Placebo: Inattentive 19.4%, Hyperactive 1.6%, Combined 79%). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (ODD 39%, elimination disorders 10%, phobias 11%, dysthymia 5%, GAD 3%, MDD 3%). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear (at least 1.5 SDs above the age and gender norms for their diagnostic subtype).
Indirectness of population	No indirectness
Interventions	<p>(n=65) Intervention 1: CNS stimulants - Atomoxetine. In the stimulant naive stratum, patients received active drug before school and in the late afternoon or early evening, as well as a midday dose of placebo. The double blind dosing schedule for patients randomised to atomoxetine allowed patients to be titrated to a maximum dose of 2mg/kg/day or a total dose of 90mg/day based on therapeutic response and tolerability. in the stimulant-prior-exposure stratum, medication was given before and after school. Duration 9 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=62) Intervention 2: No treatment - Placebo. The stimulant naive group received placebo 3 times daily, whereas the stimulant-prior-exposure group received placebo before and after school. Duration 9 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p> <p>(n=62) Intervention 3: No treatment - Placebo. The stimulant naive group received placebo 3 times daily, whereas the stimulant-prior-exposure group received placebo before and after school. Duration 9 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>

Study	Spencer 2002 ⁵⁹¹
	<p>(n=64) Intervention 4: CNS stimulants - Atomoxetine. In the stimulant naive stratum, patients received active drug before school and in the late afternoon or early evening, as well as a midday dose of placebo. The double blind dosing schedule for patients randomised to atomoxetine allowed patients to be titrated to a maximum dose of 2mg/kg/day or a total dose of 90mg/day based on therapeutic response and tolerability. In the stimulant-prior-exposure stratum, medication was given before and after school. Duration 9 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p>
Funding	Study funded by industry (Funded by Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (STUDY 1) versus PLACEBO (STUDY 1)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Treatment response (Study 1) at 9 weeks; Group 1: 42/64, Group 2: 15/61; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS total (Study 1) at 9 weeks; Group 1: mean -15.6 (SD 13.7); n=64, Group 2: mean -5.5 (SD 11.6); n=61; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS Inattentive subscale (Study 1) at 9 weeks; Group 1: mean -7.5 (SD 7.2); n=64, Group 2: mean -3 (SD 6.6); n=61; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS Hyperactive subscale (Study 1) at 9 weeks; Group 1: mean -8 (SD 7.4); n=64, Group 2: mean -2.5 (SD 5.9); n=61; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness 	
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE (STUDY 2) versus PLACEBO (STUDY 2)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Treatment response (Study 2) at 9 weeks; Group 1: 38/63, Group 2: 25/60; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS total (Study 2) at 9 weeks; Group 1: mean -14.4 (SD 13); n=63, Group 2: mean -5.9 (SD 13); n=60; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS Inattentive subscale (Study 2) at 9 weeks; Group 1: mean -7.6 (SD 7.6); n=63, Group 2: mean -3 (SD 6.8); n=60; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS Hyperactive subscale (Study 2) at 9 weeks; Group 1: mean -6.9 (SD 6.6); n=63, Group 2: mean -2.9 (SD 7.1); n=60; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at

Study	Spencer 2002⁵⁹¹
	<3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Spencer 2002⁵⁸⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	USA
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Ascertained from clinical referrals to a paediatric psychopharmacology unit.
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Any clinically significant chronic medical conditions or abnormal baseline laboratory values, low IQ (IQ <75), clinically unstable psychiatric conditions (i.e., suicidality), current bipolar disorder, psychosis, drug or alcohol abuse or dependence, or current use of other psychotropic drugs. Pregnant or nursing females were also excluded. Patients with a personal history of non-geriatric cardiac disease and transient tics were also excluded.
Recruitment/selection of patients	Patients were clinically referred
Age, gender and ethnicity	Age - Mean (SD): Desipramine: 10.6 (2.4) Placebo 11.3 (3). Gender (M:F): 34:7. Ethnicity: Not reported
Further population details	1. ADHD subtype: Combined 2. Age: Mixed (5-17 years). 3. At risk population: General population 4. Comorbidities: Mixed (Any comorbid disorder: 80%). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Tricyclic antidepressants - Amitriptyline. Medication was given as 25mg capsules, twice a day to minimise adverse effects. Study medication was titrated up to 3.5mg/kg by weeks 3 unless adverse effects developed. Duration 6 weeks. Concurrent medication/care: No subject was taking psychoactive medication within 1 month of the baseline assessment, and no additional psychoactive

Study	Spencer 2002⁵⁸⁹
	medication was allowed in the trial. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=20) Intervention 2: No treatment - Placebo. Placebo was administered as identical 25mg capsules. Duration 6 weeks. Concurrent medication/care: No subject was taking psychoactive medication within 1 month of the baseline assessment, and no additional psychoactive medication was allowed in the trial. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Funded by the Tourette's Society Association and the National Institute of Mental Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DESIPRAMINE versus PLACEBO	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Treatment response at 6 weeks; Group 1: 15/21, Group 2: 0/20; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Spencer 2008⁵⁹⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in USA; Setting: 14 centres in USA
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: meet DSM-IV criteria

Study	Spencer 2008 ⁵⁹⁷
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	DSM-IV diagnosis through k-SADS-PL assessment, ADHD-RS-IV being 1.5 SD above norms and sustained over 10-18 day period and global tic severity scale on YGTSS >5
Exclusion criteria	OCD or depression currently severe enough to warrant treatment, history of psychotic or seizure disorder, psychotropic use (apart from study drug).
Recruitment/selection of patients	not stated
Age, gender and ethnicity	Age - Mean (SD): 11.2 (2.4). Gender (M:F): 102/15. Ethnicity: Caucasian 88%, African descent 4%, Hispanic 4%, Other 4%
Further population details	1. ADHD subtype: All/mixed subtypes (Combined 65.9%, Inattentive 31%, Hyperactive/Inattentive 3%). 2. Age: Mixed (Age 7 to 17). 3. At risk population: General population 4. Comorbidities: Tic disorder and Tourette's 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: CNS stimulants - Atomoxetine. Flexible dose 0.5-1-1.5mg/kg/day (max 110mg/day regardless of weight). Duration 8 weeks. Concurrent medication/care: nil Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=56) Intervention 2: No treatment - Placebo. Placebo tablet titrated in the same way as Atomoxetine. Duration 8 weeks. Concurrent medication/care: Nil Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Co sponsored)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv total at 8 weeks; Group 1: mean -10.4 (SD 11); n=60, Group 2: mean -4.4 (SD 9.9); n=56

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2.5, Reason: Three discontinued prior to first baseline measure, one after; Group 2 Number missing: 1.5, Reason: Three discontinued prior to first baseline measure

- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv Inattention subscale at 8 weeks; Group 1: mean -5.4 (SD -6.3); n=60, Group 2: mean -2.3 (SD 6.4); n=56

Study	Spencer 2008 ⁵⁹⁷
	<p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2.5, Reason: Three discontinued prior to first baseline measure, one after; Group 2 Number missing: 1.5, Reason: Three discontinued prior to first baseline measure</p> <p>- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv Hyperactivity subscale at 8 weeks; Group 1: mean -5.1 (SD 5.7); n=60, Group 2: mean -2.1 (SD 4.8); n=56</p> <p>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2.5, Reason: Three discontinued prior to first baseline measure, one after; Group 2 Number missing: 1.5, Reason: Three discontinued prior to first baseline measure</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): Discontinuation because of adverse event at 8 weeks; Group 1: 2/61, Group 2: 1/56</p> <p>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Three discontinued prior to allocation, one after; Group 2 Number missing: 0, Reason: Three discontinued prior to allocation</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Spencer 2005 ⁵⁹⁰ (Biederman 2006) ⁹⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=146)
Countries and setting	Conducted in USA; Setting: Psychiatry Service Massachusetts General Hospital and Department of Psychiatry, Harvard Medical School
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview by age 7 as well in the last month. They must also have

Study	Spencer 2005 ⁵⁹⁰ (Biederman 2006) ⁹⁰
	described a chronic course of ADHD symptomatology from childhood to adulthood and endorsed a moderate or severe level of impairment attributed to ADHD symptoms.
Exclusion criteria	patients with clinically significant chronic medical conditions, abnormal baseline laboratory values; IQ <80, clinically unstable psychiatric conditions (bipolar disorder, psychosis, suicidality, drug or alcohol abuse, previous adequate trial of stimulant or current use of psychotropics. Pregnant and nursing women were excluded also.
Recruitment/selection of patients	Outpatient adults with ADHD aged between 19 and 60 years recruited from clinical referrals and advertisements in the local media.
Age, gender and ethnicity	Age - Median (IQR): 19-60 years. Gender (M:F): 85: 61. Ethnicity: not stated
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not defined). 2. Age: Adults 18-65 years) (19-60 years). 3. At risk population: General population 4. Comorbidities: Mixed (Major depression with at least moderate impairment (8.2%), multiple anxiety disorders (2%), at least one anxiety disorder (13%), substance abuse or dependence (0%), conduct disorder (0%), oppositional disorder (3.4%), ASP (0%)). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear (Subjects met full DSM-IV-R criteria (at least six of nine symptoms) for inattentive or hyperactive/impulsive subtypes (or both) by age 7 and within the past month).
Extra comments	ADHD sub-type not defined
Indirectness of population	No indirectness
Interventions	<p>(n=104) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Weekly supplies of Methylphenidate (MPH) were dispensed by the pharmacy in identically appearing 5 and 10 mg capsules. Study physicians prescribed medication under double blind conditions in TID dosing (7 : 30 am, noon, and 5 pm) Compliance was monitored by pill counts at each physician visit. Study medication was titrated (forced titration) up to 0.5 mg/kg/day by week 1, 0.75 mg/kg/day by week 2 and 1.0 mg/kg/day by week 3, in TID dosing unless adverse effects emerged. The dose was allowed to be increased up to a maximum of 1.3 mg/kg/ by week 5 and 6 if efficacy was partial and treatment was well tolerated. . Duration 6 weeks. Concurrent medication/care: Psychoactive medication was not permitted during the protocol Further details: 1. Dose: 2. Method of titration:</p> <p>(n=42) Intervention 2: No treatment - Placebo. Weekly supplies of placebo were dispensed by the pharmacy in identically appearing 5 and 10 mg capsules. Study physicians prescribed medication under double blind conditions in TID dosing (7 : 30 am, noon, and 5 pm) Compliance was monitored by pill counts at each physician visit. Study medication was titrated (forced titration) up to 0.5 mg/kg/day by week 1, 0.75 mg/kg/day by week 2 and 1.0 mg/kg/day by week 3, in TID dosing unless adverse effects emerged. The dose was allowed to be increased to a maximum of 1.3 mg/kg/ by week 5 and 6 if efficacy was partial and treatment was well tolerated. Duration 6 weeks. Concurrent medication/care: Psychoactive medication were</p>

Study	Spencer 2005⁵⁹⁰(Biederman 2006)⁹⁰
	not permitted during the protocol Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Study supported by funding from the National Institute of Mental Health (NIMH) and Novartis Pharmaceuticals also supported a portion of the cost. Authors also received grant support from NIMH)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MPH GROUP versus PLACEBO GROUP	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Treatment response at 6 weeks; Group 1: 59/78, Group 2: 6/32; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study	Spencer 2008⁵⁹⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in USA; Setting: 14 centres in USA
Line of therapy	1st line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: meet DSM-IV criteria
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	DSM-IV diagnosis through k-SADS-PL assessment, ADHD-RS-IV being 1.5 SD above norms and sustained over 10-18 day period and global tic severity scale on YGTSS >5
Exclusion criteria	OCD or depression currently severe enough to warrant treatment, history of psychotic or seizure disorder,

Study	Spencer 2008 ⁵⁹⁷
	psychotropic use (apart from study drug).
Recruitment/selection of patients	not stated
Age, gender and ethnicity	Age - Mean (SD): 11.2 (2.4). Gender (M:F): 102/15. Ethnicity: Caucasian 88%, African descent 4%, Hispanic 4%, Other 4%
Further population details	1. ADHD subtype: All/mixed subtypes (Combined 65.9%, Inattentive 31%, Hyperactive/Inattentive 3%). 2. Age: Mixed (Age 7 to 17). 3. At risk population: General population 4. Comorbidities: Tic disorder and Tourette's 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: CNS stimulants - Atomoxetine. Flexible dose 0.5-1-1.5mg/kg/day (max 110mg/day regardless of weight). Duration 8 weeks. Concurrent medication/care: nil Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=56) Intervention 2: No treatment - Placebo. Placebo tablet titrated in the same way as Atomoxetine. Duration 8 weeks. Concurrent medication/care: Nil Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Co sponsored)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv total at 8 weeks; Group 1: mean -10.4 (SD 11); n=60, Group 2: mean -4.4 (SD 9.9); n=56

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2.5, Reason: Three discontinued prior to first baseline measure, one after; Group 2 Number missing: 1.5, Reason: Three discontinued prior to first baseline measure

- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv Inattention subscale at 8 weeks; Group 1: mean -5.4 (SD -6.3); n=60, Group 2: mean -2.3 (SD 6.4); n=56

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2.5, Reason: Three discontinued prior to first baseline measure, one after; Group 2 Number missing: 1.5, Reason: Three discontinued prior to first baseline measure

- Actual outcome for Children (up to 18 years): ADHDRS-IV-Parent:Inv Hyperactivity subscale at 8 weeks; Group 1: mean -5.1 (SD 5.7); n=60, Group 2: mean -2.1 (SD 4.8); n=56

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Spencer 2008 ⁵⁹⁷
	- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2.5, Reason: Three discontinued prior to first baseline measure, one after; Group 2 Number missing: 1.5, Reason: Three discontinued prior to first baseline measure
	Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation because of adverse event at 8 weeks; Group 1: 2/61, Group 2: 1/56 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Three discontinued prior to allocation, one after; Group 2 Number missing: 0, Reason: Three discontinued prior to allocation
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Sutherland 2012 ⁶⁰⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=241)
Countries and setting	Conducted in USA; Setting: 8 sites in the US
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR and AISRS
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Score of 24 or more on the AISRS scale, less than 15 on the Hamilton Anxiety Rating Scale, and less than 20 on the Montgomery Asberg Depression Rating Scale.
Exclusion criteria	(1) lifetime or current history of psychosis, bipolar, intellectual disability (2) current anxiety or depressive disorders (3) substance abuse or dependence within 3 months of screening or positive urine screen for drugs of abuse at screening (4) used atomoxetine, buspirone, or a monoamine oxidase inhibitor within 2 weeks prior to screening (5) seizure disorder, urinary retention, narrow-angle glaucoma, or cardiac conduction defects (6) general medical conditions considered clinically significant as judged by the investigator (7) poor metabolizers of cytochrome or used substances with psychoactive properties and potent cytochrome inducers or inhibitors.

Study	Sutherland 2012 ⁶⁰⁷
Recruitment/selection of patients	Study conducted from November 2004 to December 2005
Age, gender and ethnicity	Age - Range: 18 to 60 years. Gender (M:F): 59% male (no further details). Ethnicity: 80% White, 10% Hispanic, 7% African American, 3% other/mixed ethnicity (approximate percentages)
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Not specified). 2. Age: Adults 18-65 years) (Mean age = 37 years, 18-60 years). 3. At risk population: General population (General population). 4. Comorbidities: Not applicable / Not stated / Unclear (Most comorbidities excluded, others not reported). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: Not applicable / Not stated / Unclear (Probably not first line). Exclusion criteria: use of atomoxetine, buspirone or a monoamine oxidase inhibitor 2 weeks prior to screening). 7. Severity: Not applicable / Not stated / Unclear (Mean scores AISRS = 36).
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	<p>(n=97) Intervention 1: CNS stimulants - Atomoxetine. Atomoxetine started at 40 mg/day and increased to 80 mg/day (40 mg every morning and 40 mg every evening) after 2 weeks. After 4 weeks the dose could be increased to 100 mg/day (60 mg morning, 40 mg evening) based on tolerability and efficacy. Mean (SD) doses were 39.1(6.1) during weeks 1 and 2, 74.6(9.6) during weeks 3 and 4, and 89.7(21.6) during weeks 5-7. 1 week period after this in which the medication was tapered and discontinued. Duration 8 weeks. Concurrent medication/care: Not specified. Some psychoactive medication formed part of the exclusion criteria. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=97) Intervention 2: Combination - See description. Atomoxetine started at 40mg/day and increased to 80mg/day (40mg every morning and 40mg every evening) after 2 weeks. After 4 weeks the dose could be increased to 100mg/day (60mg morning, 40mg evening) based on tolerability and efficacy. Buspirone was started at 15mg/day (7.5mg twice daily), increased to 30mg/day (15mg twice daily) after 1 week, and increased to 45mg/day (15mg 3 times daily) after 3 weeks. Mean (SD) doses of atomoxetine were 39.6(6.0) during weeks 1 and 2, 74.4(12.9) during weeks 3 and 4, and 90.7(20.9) during weeks 5-7. 1 week period after this in which the medication was tapered and discontinued. Duration 8 weeks. Concurrent medication/care: Not specified. Some psychoactive medication formed part of the exclusion criteria. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=47) Intervention 3: No treatment - Placebo. Placebo. No further details. Duration 8 weeks. Concurrent medication/care: Not specified. Some psychoactive medication formed part of the exclusion criteria. Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Pfizer Global Research)

Study	Sutherland 2012 ⁶⁰⁷
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Adult ADHD Investigator Rating Scale total scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Adult ADHD Investigator Rating Scale inattentive subscale change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Adult ADHD Investigator Rating Scale hyperactive/impulsive subscale change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Brown Attention Deficit Disorder scale total change scores at 8 weeks; Group 1: mean -32.3 (SD 25.6); n=97, Group 2: mean -22.2 (SD 26.3); n=47; Brown ADD scale ? Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Drop out due to adverse events at 8 weeks; Group 1: 11/97, Group 2: 7/47; Risk of bias: High; Indirectness of outcome: No indirectness <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE AND BUSPIRONE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Adult ADHD Investigator Rating Scale total change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Adult ADHD Investigator Rating Scale inattentive subscale change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Adult ADHD Investigator Rating Scale hyperactive/impulsive subscale change scores (LS mean difference, adj for baseline scores, study week, treatment group, week-by treatment interaction) at 8 weeks; Mean ; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Brown Attention Deficit Disorder scale total change scores at 8 weeks; Group 1: mean -35.4 (SD 27.7); n=97, Group 2: mean -22.2 (SD 26.3); n=47; Brown ADD scale ? Top=Unclear; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adult: Drop out due to adverse events at 8 weeks; Group 1: 15/97, Group 2: 7/47; Risk of bias: High; Indirectness of outcome: No indirectness 	
<p>Protocol outcomes not reported by the study</p>	<p>Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months</p>
<p>Risk of bias details</p>	<p>High risk of attrition bias</p>

Study	Takahashi 2009 ⁶¹⁴
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=245)
Countries and setting	Conducted in Japan; Setting: 41 study centres in Japan
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) CGI-S severity of 3+ (2) symptom score at least 1.5 SD above norm on ADHD-RS (3) normal intelligence on WISC-III.
Exclusion criteria	(1) Antipsychotics taken in the last 26 weeks (2) bipolar disorder (3) psychosis (4) history suicidal risk
Recruitment/selection of patients	Outpatients. No further details
Age, gender and ethnicity	Age - Range: 6 to 17 years. Gender (M:F): 209:36. Ethnicity: 100% Japanese
Further population details	1. ADHD subtype: All/mixed subtypes (61.2% inattentive, 4.5% hyperactive/impulsive, 34.2% combined). 2. Age: Mixed 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (46% stimulant naive). 7. Severity: Not applicable / Not stated / Unclear (1.5 SDs above ADHD-RS norms for age and gender).
Extra comments	ADHD
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: CNS stimulants - Atomoxetine. 0.5mg/kg per day, at meals (before or after) in the morning and in the evening. No further details. Duration 8 weeks. Concurrent medication/care: 54.8% had previous stimulant exposure. Randomization stratified by prior use of psychostimulants, age and ADHD subtype Further details: 1. Dose: 2. Method of titration: (n=60) Intervention 2: CNS stimulants - Atomoxetine. 1.2mg/kg per day, at meals (before or after) in the morning and in the evening. Titrated with intermediate steps: 0.5mg/kg per day, followed by 0.8mg/kg per day for 1 week. No further details. Duration 8 weeks. Concurrent medication/care: 55% had previous stimulant exposure. Randomization stratified by prior use of psychostimulants, age and ADHD subtype Further details: 1. Dose: 2. Method of titration:

Study	Takahashi 2009 ⁶¹⁴
	<p>(n=61) Intervention 3: CNS stimulants - Atomoxetine. 1.8mg/kg per day, at meals (before or after) in the morning and in the evening. 1.2mg/kg per day, at meals (before or after) in the morning and in the evening. Titrated with intermediate steps: 0.5mg/kg per day, followed by 0.8mg/kg per day for 1 week, followed by 1.2mg/kg per day for 1 week. Duration 8 weeks. Concurrent medication/care: 54.1% had previous stimulant exposure. Randomization stratified by prior use of psychostimulants, age and ADHD subtype. Further details: 1. Dose: 2. Method of titration:</p> <p>(n=62) Intervention 4: No treatment - Placebo. Placebo. Identical capsules. Duration 8 weeks. Concurrent medication/care: 51.6% had previous stimulant exposure. Randomization stratified by prior use of psychostimulants, age and ADHD subtype. Further details: 1. Dose: 2. Method of titration:</p>
Funding	Principal author funded by industry (Authors work for Eli Lilly and Company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE 0.5MG versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS-Parent Version hyperactive impulsive subscale scores - translated and validated in Japanese, rated by teachers at 8 weeks;

Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome: ADHD-RS-Parent Version Inattentive subscale - translated and validated in Japanese, rated by teachers at 8 weeks; Risk of bias: Low;

Indirectness of outcome: No indirectness

- Actual outcome: ADHD-RS-Parent Version Total Scores - translated and validated in Japanese, rated by teachers at 8 weeks; Group 1: mean -9.6 (SD 9.1); n=62, Group 2: mean -8.1 (SD 7.1); n=61; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

- Actual outcome: Discontinuation due to adverse events at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE 1.2MG versus PLACEBO

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome: ADHD-RS-Parent Version hyperactive/impulsive subscale scores - translated and validated in Japanese, rated by teachers at 8 weeks;

Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome: ADHD-RS-Parent Version inattentive subscale scores - translated and validated in Japanese, rated by teachers at 8 weeks; Risk of

bias: Low; Indirectness of outcome: No indirectness

- Actual outcome: ADHD-RS-Parent Version Total Scores - translated and validated in Japanese, rated by teachers at 8 weeks; Group 1: mean -10.8 (SD 6.8); n=58, Group 2: mean -8.1 (SD 7.1); n=61; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Takahashi 2009 ⁶¹⁴
<p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome: Discontinuation due to adverse events at 8 weeks; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE 1.8MG versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: ADHD-RS-Parent Version Total Scores - translated and validated in Japanese, rated by teachers at 8 weeks; Group 1: mean -11.6 (SD 8.8); n=60, Group 2: mean -8.1 (SD 7.1); n=61; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS-Parent Version Inattentive subscale - translated and validated in Japanese, rated by teachers at 8 weeks; Group 1: mean -6.8 (SD 5.8); n=60, Group 2: mean -4.7 (SD 4.7); n=61; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: ADHD-RS-Parent Version Hyperactive/impulsive subscale - translated and validated in Japanese, rated by teachers at 8 weeks; Group 1: mean -4.8 (SD 4.4); n=60, Group 2: mean -3.4 (SD 3.3); n=62; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome: Discontinuation due to adverse events at 8 weeks; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes low risk of bias

Study	Taylor 2000 ⁶¹⁹
Study type	RCT (Patient randomised; Crossover: 4 days)
Number of studies (number of participants)	1 (n=22)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Mixed line
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A neurological exam; clinical, developmental and childhood histories; and a semi-structured interview
Stratum	Adult

Study	Taylor 2000 ⁶¹⁹
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects had to 1. Meet full DSM-IV criteria for the disorder by the age of 7 years as well as currently, 2. Describe a chronic course of ADHD symptoms, 3. Endorse at least a moderate level of impairment from the symptoms, and 4. Provide corroborating history of the disorder from at least one parent or older sibling.
Exclusion criteria	Narcolepsy and conditions associated with altered cognitive abilities including schizophrenia, Tourette's disorder, and diagnosable neurologic conditions. Medical conditions likely to affect mood and cognition, such as metabolic disorders, mental retardation, untreated endocrine disorders, and pregnancy, precluded entry into the study. Subjects using any cannabis, cocaine, heroin or non-prescription amphetamines within 6 months of beginning drug trials were excluded. Subjects taking tricyclic antidepressants, venlafaxine, or bupropion within 3 months starting the study or prescription stimulants within 2 weeks prior to the beginning of the study were not included because of the efficacy of these drugs for ADHD symptoms would make interpretation of the results more difficult.
Recruitment/selection of patients	Health providers informed them of the study and gave them information on how to contact the clinic if they expressed interest
Age, gender and ethnicity	Age - Range: 18-59. Gender (M:F): 13:9. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Inattentive (11), Combined (9), Hyperactive (2)). 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Mixed (Depression (10), General anxiety disorder (3), Alcohol dependence (3)). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=22) Intervention 1: CNS stimulants - Dexamphetamine. Patients were given 5mg of dexamphetamine; each drug phase began with one capsule twice daily and was increased by an addition capsule twice daily every 1 to 2 days as tolerated up to four capsules per dose (a maximum of 8 capsules daily). Duration 2 weeks. Concurrent medication/care: No details given Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=22) Intervention 2: CNS stimulants - Modafinil. Patients were given 50 mg of modafinil, each drug phase began with one capsule twice daily and was increased by an addition capsule twice daily every 1 to 2 days as tolerated up to four capsules per dose (a maximum of 8 capsules daily). Duration 2 weeks. Concurrent medication/care: No details given Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=22) Intervention 3: No treatment - Placebo. Patients were given lactose; each drug phase began with one capsule twice daily and was increased by an addition capsule twice daily every 1 to 2 days as tolerated up to four capsules per dose (a maximum of 8 capsules daily). Duration 2 weeks. Concurrent medication/care: No</p>

Study	Taylor 2000 ⁶¹⁹
	details given Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMPHETAMINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: DSM-IV ADHD scale at 2 weeks; Group 1: mean 20 (SD 11.3); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: DSM-IV ADHD Inattention subscale at 2 weeks; Group 1: mean 11 (SD 6.7); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: DSM-IV ADHD Hyperactivity subscale at 2 weeks; Group 1: mean 9 (SD 5.4); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL versus DEXAMPHETAMINE</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: DSM-IV ADHD scale at 2 weeks; Group 1: mean 18.3 (SD 11.2); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: DSM-IV ADHD Inattention subscale at 2 weeks; Group 1: mean 10.5 (SD 5.3); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: DSM-IV ADHD Hyperactivity subscale at 2 weeks; Group 1: mean 7.3 (SD 6.4); n=21, Group 2: mean 12.2 (SD 6.8); n=21; Risk of bias: Low; Indirectness of outcome: No indirectness <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFANIL versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: DSM-IV ADHD scale at 2 weeks; Group 1: mean 18.3 (SD 11.2); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: DSM-IV ADHD Inattention subscale at 2 weeks; Group 1: mean 10.5 (SD 5.3); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adult: DSM-IV ADHD Hyperactivity subscale at 2 weeks; Group 1: mean 7.3 (SD 6.4); n=21, Risk of bias: Low; Indirectness of outcome: No indirectness 	

Study	Taylor 2000 ⁶¹⁹
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Taylor 2001 ⁶²⁰
Study type	RCT (Patient randomised; Crossover: 4 days)
Number of studies (number of participants)	1 (n=17)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects had to meet DSM-IV criteria for the disorder from 7 years old on with a corroborating history from at least one relative
Exclusion criteria	Conditions already associated with frontostriatal pathology, including organic brain disorders, schizophrenia, and Tourette disorder. Medical conditions likely to affect mood or cognition, such as metabolic disorders, central nervous system conditions, mental retardation, untreated endocrine disorders, and pregnancy precluded entry into the study. Subjects using substances such as cannabis, amphetamines, cocaine, and heroin within 6 months of beginning drug trials were excluded. Subjects taking tricyclics, venlafaxine, or bupropion within 3 months, or stimulants within 2 weeks, before the beginning of the study were not included because the efficacy of these drugs for ADHD symptoms would make the interpretation of the results more difficult.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 41.2 (11.4). Gender (M:F): 7:10. Ethnicity: No details
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Adults 18-65 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear

Study	Taylor 2001 ⁶²⁰
Indirectness of population	No indirectness
Interventions	<p>(n=17) Intervention 1: CNS stimulants - Dexamphetamine. Patients received 2.5mg of guanfacine, the dosing schedule began with one capsule and was increased by an additional capsule every day to 2 days, as tolerated up to 20 mg. Duration 2 weeks. Concurrent medication/care: No concomitant medication was permitted Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=17) Intervention 2: Guanfacine. Patients received 0.25 mg of guanfacine, the dosing schedule began with one capsule and was increased by an additional capsule every day to 2 days, as tolerated up to 2 mg. Duration 2 weeks. Concurrent medication/care: No concomitant medication was permitted Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=17) Intervention 3: No treatment - Placebo. Placebo capsules contained lactose. Duration 2 weeks. Concurrent medication/care: No concomitant medication was permitted Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMPHETAMINE versus GUANFACINE

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: ADHD DSM-IV total score at 2 weeks; Group 1: mean 24.2 (SD 12); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: ADHD DSM-IV hyperactivity subscale at 2 weeks; Group 1: mean 10.2 (SD 6.4); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: ADHD DSM-IV inattentive subscale at 2 weeks; Group 1: mean 14 (SD 6.1); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: ADHD DSM-IV total score at 2 weeks; Group 1: mean 24.2 (SD 12); n=17, Group 2: mean 30.4 (SD 10.6); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adult: ADHD DSM-IV hyperactivity subscale at 2 weeks; Group 1: mean 10.2 (SD 6.4); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness

Study	Taylor 2001 ⁶²⁰
<p>- Actual outcome for Adult: ADHD DSM-IV inattentive subscale at 2 weeks; Group 1: mean 14 (SD 6.1); n=17, Group 2: mean 17.2 (SD 5.2); n=17; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <p>- Actual outcome for Adult: ADHD DSM-IV total score at 2 weeks; Group 1: mean 22.3 (SD 8.2); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adult: ADHD DSM-IV hyperactivity subscale at 2 weeks; Group 1: mean 9.5 (SD 5); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adult: ADHD DSM-IV inattentive subscale at 2 weeks; Group 1: mean 12.8 (SD 4.1); n=17, Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Tenenbaum 2002 ⁶²⁴
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in USA; Setting: The Attention Deficit Center, St Louis
Line of therapy	Unclear
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV as operationalised by clinical interview and standard rating scales
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Any clinically significant medical conditions such as heart condition, untreated thyroid condition, or tic disorder. Participants with active substance or alcohol abuse/dependence in the six months preceding the

Study	Tenenbaum 2002 ⁶²⁴
	study were also excluded. Pregnant or nursing females were excluded on the basis of self-report. Other criteria included neurological trauma or disorder (e.g. concussion, epilepsy), chronic diseases, poor physical health, and poor vision (unless corrected). Individuals who were taking psychoactive medication (including methylphenidate) were excluded from the study unless they discontinued such medications under the supervision of their prescribing physician for the duration of the study.
Recruitment/selection of patients	Subjects were recruited via newspaper advertisements, outpatient therapy practices, support groups and posted notices
Age, gender and ethnicity	Age - Range: 24-53. Gender (M:F): 11:13. Ethnicity: Caucasian (100%)
Further population details	1. ADHD subtype: Combined 2. Age: Adults 18-65 years) (24-53). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV as operationalised by clinical interview and standard rating scales). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Unclear line of therapy
Interventions	<p>(n=24) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . On treatment days 1 and 2, MPH was given as 5mg in the morning and at lunch; placebo was given at 4pm and in the evening. On days 3 and 4, 5mg was given in the morning, at lunch and at 4pm; placebo was given in the evening. On days 5-7 10mg was given in the morning and at lunch, 5mg was given at 4pm and placebo given in the evening. On days 8-10, 10mg was given in the morning, at lunch and 4pm whilst placebo was given in the evening. On days 11-13, 15mg was given in the morning and at lunch, 10mg was given at 4pm and placebo in the evening. On days 14-21, 15mg was given three times a day and placebo in the evening. Duration 3 weeks. Concurrent medication/care: Patients were advised to discontinue any psychoactive medication they were previously taking during the study period Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Mixed (Titrated to fixed dose).</p> <p>(n=24) Intervention 2: No treatment - Placebo. Placebo was administered four times a day. Duration 3 weeks. Concurrent medication/care: Patients were advised to discontinue any psychoactive medication they were previously taking during the study period Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Funded by Henkel Corporation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO

Study	Tenenbaum 2002 ⁶²⁴
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: Barkley's ADHD Rating Scale at 3 weeks; Group 1: mean 2.08 (SD 2.6); n=24, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of attrition bias

Study	Tramontina 2009 ⁶³⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in Brazil; Setting: hospital de Clinicas de Porto Alegre, Rio Grande do Sul, Brazil
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years): children
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 8-17 years, DSM IV Bipolar 1 or 2 disorder comorbid with DSM-IV ADHD, clear reports of ADHD symptom onset preceding any mood symptomatology and acutely manic or mixed state defined as Young Mania Rating Scale score >20 at baseline
Exclusion criteria	Estimated IQ lower than 7- assessed using the Wechsler Intelligence Scale for Children by a trained psychologist, use of any medication 4 weeks prior to entering the study, diagnosis of pervasive developmental disorder, schizophrenia, or substance abuse or dependence, severe suicide/homicide risk contraindicating outpatient treatment, previous use of aripiprazole, any other acute or chronic disease that might interfere with the study and pregnancy.
Recruitment/selection of patients	Recruitment was performed in the community through press releases. Initial assessment involved telephone interview conducted by a child psychiatrist for identification of eligible candidates. After primary care givers

Study	Tramontina 2009⁶³⁰
	had endorsed symptoms of bipolar disorder and ADHD according to DSM-IV, children, adolescent and their parents underwent a further 3 stage confirmatory process involving further evaluation
Age, gender and ethnicity	Age - Range: 8-17 years. Gender (M:F): 20/23. Ethnicity: 90.7% white, 9.30% other
Further population details	1. ADHD subtype: All/mixed subtypes (79% of patients were of combined subtype of ADHD and 21% of either inattentive or hyperactive/impulsive subtype). 2. Age: Mixed (8-17 years). 3. At risk population: Not applicable / Not stated / Unclear (Not reported). 4. Comorbidities: Mixed (100% of participants were diagnosed with bipolar disorder. 37% of patients had comorbid psychosis symptoms, 48.8% had anxiety disorders and 81.4% had comorbid disruptive behavioural disorders). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear line of treatment; response not an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear (Mean SNAP-IV score = 2.21 (intervention) and 2.02 (control); scale = 0-3)).
Indirectness of population	Serious indirectness: Unclear line
Interventions	(n=18) Intervention 1: Antipsychotics - Aripiprazole. Patients initially received a weekly supply of aripiprazole based on their weight. Subjects weighing more than 50 kg received a 5 mg starting dose, while those weighing less received 2 mg dose. Patients were assessed weekly for 6 weeks and doses were increased 5mg/weekly according to clinical response and onset of adverse events until a maximum dose of 20 mg/d was reached. Duration 6 weeks. Concurrent medication/care: No concomitant treatment was allowed during study Further details: 1. Dose: Not applicable / Not stated / Unclear (Mean final dose = 13.61mg (SD = 5.37; range = 5-20mg)). 2. Method of titration: Titrated to optimum dose (Titrated to optimum dose based on response and side effects). (n=25) Intervention 2: No treatment - Placebo. Matching placebo to active treatment. Duration 6 weeks. Concurrent medication/care: No concomitant treatment allowed Further details: 1. Dose: 2. Method of titration:
Funding	Equipment / drugs provided by industry (part funded by Bristol-Myers Squib)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Swanson, Nolan and Pelham Scale-version IV (SNAP-IV); adjusted for baseline SNAP-IV score and type of ADHD at 6 weeks; Group 1: mean 0.79 (SD 0.87092); n=17, Group 2: mean 0.55 (SD 0.87082); n=24; Risk of bias: Very High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): CGI-Severity at 6 weeks; Group 1: mean 2.05 (SD 0.60872); n=17, Group 2: mean 1.64 (SD 0.60872);

Study	Tramontina 2009⁶³⁰
n=24; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: very high risk of bias due to (1) selection bias (differences at baseline in sex, race and bipolar disorder type) and (2) outcome reporting bias; standard deviation was not reported and was estimated.

Study	Van der Heijden 2007⁶³⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in Netherlands; Setting: Outpatient clinics at the Gelderse Vallei General Hospital and Kempenhaeghe by seven Dutch community mental health institutions and three paediatric hospital departments
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV criteria assessed using structured interview
Stratum	Children (up to 18 years): Children
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged between 6-12 years, diagnosis of ADHD and chronic sleep-onset insomnia (SOI) as well as written informed consent from parents
Exclusion criteria	Total IQ<8-, pervasive developmental disorder, chronic pain, known disturbed hepatic or renal function, epilepsy, earlier use of melatonin and use of stimulants, neuroleptics, clonidine, antidepressants, hypnotics or beta blockers within 4 weeks before enrolment
Recruitment/selection of patients	Children with possible ADHD were referred for participation to outpatient clinics for sleep-wake disorders of the Gelderse Vallei General Hospital and Kempenhaeghe by seven Dutch community mental health institutions and three paediatric hospital departments. 20 children were also recruited through advertisements in magazines, newspapers or via the Dutch ADHD patient support Centre.

Study	Van der Heijden 2007 ⁶³⁸
Age, gender and ethnicity	Age - Range: 6-12 years. Melatonin Group- mean (SD)=9.1(2.3) and Placebo -mean (SD)=9.3 (1.8). Gender (M:F): 78/27. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (73% of patients were of combined subtype of ADHD, 21% of patients were of the inattentive subtype and 3.8% were of the hyperactive/impulsive subtype). 2. Age: Children (6-12 years) (Children 6-12 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Mixed (All children had chronic sleep-onset insomnia. Approximately 63% of children had a psychiatric comorbidity including disruptive behavioural disorder, anxiety disorder and depressive disorder). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear line. Response not an exclusion criteria.). 7. Severity: Not applicable / Not stated / Unclear (Not reported).
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Melatonin. 3 mg of Melatonin when body weight <40 kg (n=44), 6 mg when body weight was > 40 kg (n=9) in fast-release tablets at 7 pm. Duration 4 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration: (n=53) Intervention 2: No treatment - Placebo. Identical appearing tablets as active treatment at 7 pm. Duration 4 weeks. Concurrent medication/care: None reported Further details: 1. Dose: 2. Method of titration:
Funding	Academic or government funding (Maarteb Kapelle Foundation and Foundation De Drie Lichten)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MELATONIN GROUP versus PLACEBO GROUO

Protocol outcome 1: Quality of life at <3- or >6-months

- Actual outcome for Children (up to 18 years): TNO-AZL Questionnaire for Children's Health Related Quality of Life, Parent form (TACQOL-P) at 4 weeks; Group 1: mean 179.1 (SD 21.8); n=53, Group 2: mean 176.9 (SD 22.5); n=52; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Behavioural outcomes at <3- or >6-months

- Actual outcome for Children (up to 18 years): Child Behaviour Check List (CBCL) at 4 weeks; Group 1: mean 55.1 (SD 18.4); n=53, Group 2: mean 45.3 (SD 25.7); n=52; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): Teacher's report form (TRF) at 4 weeks; Group 1: mean 42.1 (SD 19.1); n=53, Group 2: mean 48.1 (SD 25); n=52; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 4 weeks; Group 1: 0/53, Group 2: 0/52; Risk of bias: Low;

Study	Van der Heijden 2007 ⁶³⁸
Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

Study	Wang 2007 ⁶⁴⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=330)
Countries and setting	Conducted in China, Mexico, South Korea; Setting: Not stated
Line of therapy	Mixed line
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical interview and K-SADS-PL
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children and adolescents aged 6-16, weighing between 20 and 60 kg who met DSM-IV criteria for ADHD, with a score of ≥ 25 for boys or ≥ 22 for girls, or > 12 for a specific subtype, on the ADHDRS-IV Parent:Inv as well as a CGI-S score of ≥ 4
Exclusion criteria	Any history of bipolar, psychotic or pervasive developmental disorders; suicidal risk; or ongoing use of psychoactive medications other than the study drug. Patients with motor tics, a diagnosis or family history of Tourette's syndrome or those who met DSM-IV criteria for anxiety disorder
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 6-16. Gender (M:F): 270:60. Ethnicity:
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Mixed (6-16). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=164) Intervention 1: CNS stimulants - Atomoxetine. Therapy began at 0.8mg/kg/day administered once

Study	Wang 2007⁶⁴⁶
	<p>daily in the morning which was titrated to 1.2mg/kg/day on day 5, and could be either maintained or titrated upward or downward within the final range of 0.8-1.8mg/kg/day. Duration 8 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=166) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). Therapy began at 0.2mg/kg/day administered twice daily, which was titrated to 0.4mg/kg/day on day 5 and could be maintained or titrated upwards or downward within the final range of 0.2-0.6mg/kg/day. Duration 8 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHDRS-IV Hyperactivity subscale at 8 weeks; Group 1: mean -9.7 (SD 5.8); n=162, Group 2: mean -9.5 (SD 5.5); n=164; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHDRS-IV Inattention subscale at 8 weeks; Group 1: mean -11.3 (SD 5.7); n=162, Group 2: mean -12 (SD 5.4); n=164; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHDRS-IV Total score at 8 weeks; Group 1: mean -21.1 (SD 10.3); n=162, Group 2: mean -21.6 (SD 9.6); n=164; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): CPRS Oppositional subscale at 8 weeks; Group 1: mean -3 (SD 3.9); n=162, Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation due to adverse events at 8 weeks; Group 1: 18/164, Group 2: 6/166; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcome 1-2: High risk of bias

Study	Wang 2007⁶⁴⁶
	Protocol outcome 3: Low risk of bias

Study	Weiss 2005⁶⁶²
Study type	RCT (Site randomised; Parallel)
Number of studies (number of participants)	1 (n=153)
Countries and setting	Conducted in Canada, Puerto Rico, USA; Setting: Eight investigative sites in the United States, two in Canada and one site in Puerto Rico
Line of therapy	Unclear
Duration of study	Intervention time: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Subjects were evaluated by clinical assessment and confirmed using a structured parent interview/
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 8-12 years with ADHD as defined by DSM-IV were eligible to participate. Diagnostic criteria were evaluated by clinic assessment and confirmed using a structured parent interview, the behavioural module of the Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version. ADHD symptoms had to be at least 1 SD above age and sex norms on the ADHD-RS-IV-Teacher version: Investigation administered and scored. Patients were also required to have a mean Conners Parent Rating Scale ADHD Index score at least 1.5 SDs above age and sex norms.
Exclusion criteria	Unavailability of a primary teacher willing to keep telephone appointments and to provide ratings and reports as part of the study, evidence of a significant intellectual deficit, serious medical illness, or use of other psychotropic medication.
Recruitment/selection of patients	Community advertisements were used to aid in patient recruitment
Age, gender and ethnicity	Age - Range: 8-12 years. Gender (M:F): 123/30. Ethnicity:
Further population details	1. ADHD subtype: All/mixed subtypes (Hyperactive/impulsive 0.7%, Inattentive 26.8%, 72.5%). 2. Age: Children (6-12 years) (8-12 years). 3. At risk population: General population 4. Comorbidities: Mixed (ODD 33.3%, Generalised anxiety disorder 2.6%, Learning disorder 29.8%, Motor skills disorder 6.5%, Communications disorder 8.1%). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) 7. Severity: Not applicable / Not stated / Unclear (At least 1.0 SDs above age and sex norms on ADHD-RS-IV-T and CPRS-RS score at least 1.5 SDs above age sex and norms).
Indirectness of population	No indirectness

Study	Weiss 2005 ⁶⁶²
Interventions	<p>(n=101) Intervention 1: CNS stimulants - Atomoxetine. Patients assigned to atomoxetine received 0.8mg/kg/day in the morning for 3 days, after which the dose was increased to 1.2mg/kg/day. After 3 weeks, patients with significant residual symptomatology (defined as a CGI-S score of 3 or more) and for whom there was no safety or tolerability contraindication could have their dose increased to 1.8mg/kg/day. Duration 7 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose</p> <p>(n=52) Intervention 2: No treatment - Placebo. Subjects were given study medication identical in appearance to atomoxetine. Duration 7 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Principal author funded by industry (Drs Tannock, Weiss, Kratochvil, Dunn and Velez-Borras were paid consultants and/or investigators for studies sponsored by ELi Lilly and company)

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

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Children (up to 18 years): CGI-I at 7 weeks; Group 1: mean 2.6 (SD 1); n=99, Group 2: mean 3.4 (SD 1); n=51; Clinical global impressions scale 1-7 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): Treatment response at 7 weeks; Group 1: 69/100, Group 2: 22/51; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS Inattentive subscale Teacher rated at 7 weeks; Group 1: mean -7.5 (SD 7.4); n=100, Group 2: mean -4.3 (SD 6.2); n=51; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS Hyperactive/impulsive subscale Teacher rated at 7 weeks; Group 1: mean -7 (SD 6.3); n=100, Group 2: mean -3 (SD 5.3); n=51; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS total score at 7 weeks; Group 1: mean -14.5 (SD 12.3); n=100, Group 2: mean -7.2 (SD 9.7); n=51; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Discontinued due to adverse events at 7 weeks; Group 1: 6/101, Group 2: 0/52; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Academic outcomes (literacy and numeracy) at <3- or >6-months

Study	Weiss 2005 ⁶⁶²
	- Actual outcome for Children (up to 18 years): Academic Performance Rating Scale at 7 weeks; Group 1: mean 4.8 (SD 9.2); n=70, Group 2: mean 2.2 (SD 9.6); n=36; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Protocol outcomes 1, 2 and 4: High risk of bias due to attrition Protocol 3: Low risk of bias

Study	Wender 1985 ⁶⁶⁵
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Semi-structured personal and family history instrument, including questions appropriate for diagnosis according to DSM-III criteria
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects must have had a history of attention deficit disorder with hyperactivity and attentional deficit persisting from childhood. In addition, he or she must have had two of the following characteristics: 1) affective lability, 2) inability to complete tasks, 3) hot or explosive temper, 4) impulsivity, and 5) stress intolerance
Exclusion criteria	Subjects that had never met DSM-III criteria for schizophrenia or schizoaffective disorder, currently had no mood disorder (including mild forms), and had none of the schizoid, schizotypal, or borderline personality disorder, such as unstable and intense interpersonal relationships with idealisation and devaluation, identity disturbances, intolerance of being alone, and physically self-damaging acts, including self-mutilation and suicidal gestures.
Recruitment/selection of patients	Collaboration with the Salt Lake Community Mental Health Center which has a catchment area of about 200,000 people, and with local psychiatrists, psychologists, and social workers in private practice.
Age, gender and ethnicity	Age - Mean (SD): 31.1 (6.7). Gender (M:F): 20:17. Ethnicity: White (100%)

Study	Wender 1985 ⁶⁶⁵
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear (Residual type). 2. Age: Adults 18-65 years) (Mean (SD): 31.1 (6.7)). 3. At risk population: General population 4. Comorbidities: Mixed (Dysthymic disorder (68%), cyclothymic disorder (22%), and generalised anxiety disorder (11%)). 5. Diagnostic method: DSM (Semi-structured personal and family history instrument, including questions appropriate for diagnosis according to DSM-III criteria). 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	Serious indirectness: Unclear line of therapy
Interventions	(n=37) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). The initial dose was 5mg at 8am and noon, increased by 5mg per dose every 2-3 days on the basis of the patient's report. The maximum dose was set at three tablets three times a day. Duration 2 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Titrated to optimum dose (n=37) Intervention 2: No treatment - Placebo. Placebo tablets were dispensed at 10mg tablets identical to methylphenidate tablets. Duration 2 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Funded in part by NIMH grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO	
Protocol outcome 1: Behavioural outcomes at <3- or >6-months - Actual outcome for Adult: Global Assessment Scale at 2 weeks; Group 1: mean 69.17 (SD 9.66); n=37, Group 2: mean 61.26 (SD 8.02); n=37; Global Assessment Scale 0-100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	High risk of bias due to attrition bias

Study	Wernicke 2004 ⁶⁶⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	4 (n=Children - 200 Adults - 284)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	Children: School aged children who met DSM-IV criteria for the diagnosis of ADHD. Adults: Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: Children 7-12, Adults unclear. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. ADHD subtype: Not applicable / Not stated / Unclear 2. Age: Mixed (Children 7-12 years, Adults). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=102) Intervention 1: CNS stimulants - Atomoxetine. The studies included a 2 week evaluation/washout period followed by approximately 9 weeks of double blind treatment with either atomoxetine (titrated based on clinical response to a maximum dose of 2mg/kg/d and administered as evenly divided dose twice daily) or placebo. Duration 9 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration: Titrated to optimum dose</p> <p>(n=92) Intervention 2: No treatment - Placebo. The studies included a 2 week evaluation/washout period followed by approximately 9 weeks of double blind treatment with either atomoxetine (titrated based on clinical response to a maximum dose of 2mg/kg/d and administered as evenly divided dose twice daily) or placebo. Duration 9 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration:</p>

Study	Wernicke 2004⁶⁶⁶
	<p>(n=195) Intervention 3: No treatment - Placebo. For patients receiving atomoxetine, dosing was initiated at 30mg twice a day, and titrated based on clinical response to a maximum of 60mg twice a day. Duration 10 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration: Titrated to optimum dose</p> <p>(n=89) Intervention 4: CNS stimulants - Atomoxetine. For patients receiving atomoxetine, dosing was initiated at 30mg twice a day, and titrated based on clinical response to a maximum of 60mg twice a day. Duration 10 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration: Titrated to optimum dose</p>
Funding	Study funded by industry (Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE - CHILDREN versus PLACEBO - CHILDREN</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: ADHD-RS at 9 weeks; Group 1: mean -17.2 (SD 12.6); n=102, Group 2: mean -6.4 (SD 12.4); n=92; ADHD Rating Scale 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE - ADULTS versus PLACEBO - ADULTS</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: CAARS total score at 10 weeks; Group 1: mean -11.2 (SD 10.7); n=89, Group 2: mean -7 (SD 9.5); n=195; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: very high risk of bias. Various details are not reported across multiple domains; including exclusion criteria, allocation concealment, baseline characteristics and attrition rates.

Study	Wietecha 2009⁶⁷¹ (Wietecha 2013⁶⁶⁹; Saylor 2009⁵⁵¹)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of	1 (n=209)

Study	Wietecha 2009 ⁶⁷¹ (Wietecha 2013 ⁶⁶⁹ ; Saylor 2009 ⁵⁵¹)
participants)	
Countries and setting	Conducted in USA; Setting: multicentre trial- no other information provided
Line of therapy	Unclear
Duration of study	Intervention time: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessed for DSM-IV criteria in structured interview by research team
Stratum	Children (up to 18 years): Children with ADHD and Dyslexia
Subgroup analysis within study	Stratified then randomised: Population: children with ADHD and dyslexia, amongst a wider sample of children with ADHD. Subgroup data only reported here.
Inclusion criteria	DSM-IV diagnosis of ADHD confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version. ADHD-RS-IV scores had to be 1.5+ SDs above age and gender norms. Participants with dyslexia were required to have a 22+ point discrepancy between the WASI Verbal Intelligence Quotient or Performance Intelligence Quotient (whichever was higher) and the Woodcock Jonson III Basic Reading Skills score, Letter Word Identification score, or Word Attack score, or a score of 89 or less on any of the Woodcock Johnson III subscales
Exclusion criteria	(1) history of bipolar I or II, psychosis, autism, Asperger's syndrome, pervasive developmental disorder (2) taking anticonvulsants for seizure control
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 10 to 16 years. Gender (M:F): 3:1. Ethnicity: 11.48% African American, 72.72% White, 0.014% Eastern Asian, 13.88% Hispanic, 0.005% West Asian
Further population details	1. ADHD subtype: All/mixed subtypes (40.67% inattentive, 36.84 combined, 1.91% hyperactive/impulsive). 2. Age: Mixed (Range = 10-17 years, mean = 12.2 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Intellectual disability (Dyslexia). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) (<70% of participants are drug naive). 7. Severity:
Indirectness of population	--
Interventions	(n=120) Intervention 1: CNS stimulants - Atomoxetine. 0.5mg/kg/day for 3 days followed by 1-1.4mg/kg/day. Administered once a day with food. No further details. Duration 16 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration: (n=89) Intervention 2: No treatment - Placebo. Placebo. Duration 16 weeks. Concurrent medication/care: No details Further details: 1. Dose: 2. Method of titration:

Study	Wietecha 2009⁶⁷¹ (Wietecha 2013⁶⁶⁹; Saylor 2009⁵⁵¹)
Funding	Study funded by industry (Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHD+DYSLEXIA (ATOMOXETINE)-ACUTE PHASE versus PLACEBO (ACUTE PHASE)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD-RS-IV Parent Version: Inv Total Scores (least square mean adjusted for baseline) at 16 weeks; Group 1: mean -18.07 (SD 41.15); n=62, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Teacher Version: Inv total scores (least square mean adjusted for baseline) at 16 weeks; Group 1: mean -8.26 (SD 10.3859); n=21, Group 2: mean -3.6 (SD 10.3859); n=22; ADHD-RS-Teacher 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Teacher Version: Inv Hyperactive subscale (least square mean adjusted for baseline) at 16 weeks; Group 1: mean -3.03 (SD 6.87142); n=21, Group 2: mean -2.52 (SD 6.87142); n=22; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Teacher Version: Inv Inattentive subscale (least square mean adjusted for baseline) at 16 weeks; Group 1: mean -5.24 (SD 5.8171); n=21, Group 2: mean -1.08 (SD 5.8171); n=22; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Parent Version: Inv Inattentive subscale (least square mean adjusted for baseline) at 16 weeks; Group 1: mean -9.82 (SD 6.94); n=62, Group 2: mean -6.83 (SD 6.94); n=58; ADHD-RS 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV Parent Version: Inv Hyperactive subscale (least square mean adjusted for baseline) at 16 weeks; Group 1: mean -7.71 (SD 5.6634); n=62, Group 2: mean -4.44 (SD 5.6634); n=58; Risk of bias: Very high; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Very high risk of bias due to attrition and selection bias

Study	Wehmeier 2011⁶⁵⁷
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Study	Wehmeier 2011 ⁶⁵⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=128)
Countries and setting	Conducted in Germany; Setting: 16 study sites across Germany
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6 to 12 years with a diagnosis of ADHD according to DSM-IV-TR
Exclusion criteria	(1) previous treatment with atomoxetine or psychotropic medication other than the study drug (2) over or underweight (2) history of bipolar disorder, psychosis, PDD, seizure disorder (other than febrile seizures), serious suicidal risk, and any other relevant acute or unstable medical condition.
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Range: 6 to 12 years. Gender (M:F): 97:28. Ethnicity: Not specified
Further population details	1. ADHD subtype: All/mixed subtypes 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (40% ODD or CD). 5. Diagnostic method: DSM 6. Line of treatment: Not applicable / Not stated / Unclear 7. Severity: Mixed
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: CNS stimulants - Atomoxetine. Medication was given once daily in the morning. Titration was initiated at 0.5mg/kg per day for 1 week, followed by 7 weeks on the standard target dose of 1.2mg/kg per day. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration: (n=62) Intervention 2: No treatment. Matching placebo. Duration 8 weeks. Concurrent medication/care: Not specified Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Eli Lilly and Company)

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

Study	Wehmeier 2011 ⁶⁵⁷
	<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS total score (LS mean difference) at 8 weeks; MD; 11.6 (95%CI 8.2 to 15.99) ADHD-RS 0-54 Top=High is poor outcome;</p> <p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 11</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS hyperactivity subscale score (LS mean difference) at 8 weeks; MD; 6.55 (95%CI 4.74 to 8.35) ADHD-RS 0-27 Top=High is poor outcome;</p> <p>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 11</p> <p>- Actual outcome for Children (up to 18 years): ADHD-RS inattention subscale score (LS mean difference) at 8 weeks; MD; 5.12 (95%CI 3.3 to 6.94) ADHD RS 0-27 Top=High is poor outcome;</p> <p>Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <p>- Actual outcome for Children (up to 18 years): Dropped out due to adverse events at 8 weeks; Group 1: 3/63, Group 2: 2/62</p> <p>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 ; Group 1 Number missing: 9; Group 2 Number missing: 11</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Wehmeier 2012 ⁶⁵⁶ (Wehmeier 2015 ⁶⁵⁴ , Wehmeier 2014 ⁶⁵²)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=125)
Countries and setting	Conducted in Germany; Setting: 16 study sites located all over Germany included 3 university departments for child and adolescent psychiatry, 1 non-university hospital for child and adolescent psychiatry, and 12 office-based practices for child and adolescent psychiatry and/or paediatrics.
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)

Study (subsidiary papers)	Wehmeier 2012 ⁶⁵⁶ (Wehmeier 2015 ⁶⁵⁴ , Wehmeier 2014 ⁶⁵²)
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible were girls and boys aged 6 to 12 years with a diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, criteria. The diagnosis was confirmed using the Diagnose-Checklist Hyper Hyperkinetische Disorders), a structured instrument that is routinely used for the diagnostic assessment of ADHD in Germany.12 The items of this instrument correspond to those of the ADHD Rating Scale (ADHD-RS)
Exclusion criteria	Exclusion criteria comprised previous treatment with ATX, treatment with psychotropic medication other than the study drug, clinically relevant overweight and underweight, a history of bipolar disorder, psychosis, pervasive developmental disorder, seizure disorder (other than febrile seizures), serious suicidal risk, and other relevant acute or unstable medical condition. Psychotherapy initiated before the study was acceptable
Recruitment/selection of patients	Study recruited from October 2007 to May 2009. No other details reported
Age, gender and ethnicity	Age - Mean (SD): 9.0 (1.79) Range: 6-12 years. Gender (M:F): 97/28. Ethnicity: 99% white, 1% not reported
Further population details	1. ADHD subtype: All/mixed subtypes (70.4% of the study population included patients with combined subtype of ADHD, 22.4% with predominantly inattentive subtype and 0.8% with predominantly hyperactive/impulsive subtype). 2. Age: Children (6-12 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Mixed (31.2% oppositional defiant disorder, 16.8% conduct disorder). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (75.2% of the study population were stimulant naive, previous treatment with atomoxetine was an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear
Extra comments	70.4% of the study population included patients with combined subtype of ADHD, 22.4% with predominantly inattentive subtype and 0.8% with predominantly hyperactive/impulsive subtype. 40% of the study population also had at least 1 psychiatric comorbidity which included 31.2% having ODD, 16.8% conduct disorder, 40% with a combination of ODD and conduct disorder, 0.8% with tic disorder and mood disorder
Indirectness of population	No indirectness
Interventions	<p>(n=63) Intervention 1: CNS stimulants - Atomoxetine. Treatment with ATX starting at 0.5 mg/kg per day for 1 week, followed by 7 weeks on the standard target dosage of 1.2 mg/kg per day. Medication was given once daily in the morning. The cb-CPT plus MT was carried out in the morning (before taking the medication), at noon, and in the late afternoon/early evening on visit days. Duration 8 weeks. Concurrent medication/care: none reported Further details: 1. Dose: 2. Method of titration:</p> <p>(n=62) Intervention 2: No treatment - Placebo. Matching Placebo to active treatment. Duration 8 weeks. Concurrent medication/care: Not reported Further details: 1. Dose: 2. Method of titration:</p>

Study (subsidiary papers)	Wehmeier 2012 ⁶⁵⁶ (Wehmeier 2015 ⁶⁵⁴ , Wehmeier 2014 ⁶⁵²)
Funding	Study funded by industry (Lilly Deutschland , German affiliate of Eli Lilly and Company)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE GROUP versus PLACEBO GROUP</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): ADHD RS Total score-Least square mean difference at 8 weeks; MD 11.60 (standard error 1.73); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CGI-S-Least square mean difference at 8 weeks; MD 1.11 (Standard error 0.18); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Weekly Ratings of Morning and Evening Behaviour -Revised Investigator rated (WREMB-R-Inv)-Least square mean difference at 8 weeks; MD 5.74 (standard error 1.11); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CGI-S-comparison of subjects with or without ODD/CD at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): WREMB-R-Inv -comparison of subjects with or without ODD/CD at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD RS Total score-comparison of subjects with or without stimulant pre-treatment at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): CGI-S-comparison of subjects with or without stimulant pre-treatment at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Weekly Rating of Evening and Morning Behaviour (WREMB-R-Inv) -comparison of subjects with or without stimulant pre-treatment at 8 weeks; Risk of bias: ; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): Weekly Rating of Evening and Morning Behaviour (WREMB-R)-Total Score (Least Square Mean Difference) at 8 weeks; MD 5.74 (Standard Error 1.11); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-Total Score (Least Square Mean Difference) at 8 weeks; MD 11.60 (Standard error 1.73); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-Hyperactivity(Least Square Mean Difference) at 8 weeks; MD 6.55 (Standard error 0.92); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-Inattention(Least Square Mean Difference) at 8 weeks; MD 5.12 (Standard error 0.93); Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Children (up to 18 years): Adverse events leading to discontinuation at 8 weeks; Group 1: 2/63, Group 2: 3/62; Risk of bias: High; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months;

Study (subsidiary papers)	Wehmeier 2012⁶⁵⁶ (Wehmeier 2015⁶⁵⁴, Wehmeier 2014⁶⁵²)
study	Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes high risk of bias due to attrition bias

Study	Wilens 2008⁶⁸⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=147)
Countries and setting	Conducted in Canada, USA; Setting: Multicentre trial conducted in 14 sites (13 in the US and 1 in Canada)
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR + AISRS
Stratum	Adult: Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Subjects >18 years of age meeting DSM-IV-TR criteria for ADHD (any subtype) and ADHD symptoms > 20 on the AISRS. (2) subjects also met DSM-IV-TR criteria for alcohol use disorders (abuse or dependence) (3) other substance use did not preclude participation provided that the primary substance the patient abused or had dependence on was alcohol and that subjects were not actively abusing other substances at study entry (4) all subjects included were alcohol free for at least 4 days before randomisation but not longer than 30 days. The minimum four abstinent days had to be consecutive and overlap with the week before randomisation
Exclusion criteria	Patients with a diagnosis of current bipolar disorder, major depressive disorder or psychosis were excluded as well as subjects with significant cognitive impairment.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: >18 years. Mean (SD)= 34.3 (10.2) in Atomoxetine group and 34.8 (9.9) in Placebo. Gender (M:F): 125/22. Ethnicity: 88% Caucasian, 4% African descent, 0.7% Asian, 6% Hispanic and 1.4% other
Further population details	1. ADHD subtype: All/mixed subtypes (83.7%=combined subtype, 1.36%= hyperactive/impulsive and 14.3%= inattentive). 2. Age: Not applicable / Not stated / Unclear (Adults aged >18 years. Unclear if any adults >65 years were included.). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Addiction (44.2% of the subjects in the trial had an alcohol abuse disorder and 55.8% had alcohol dependence. No other co-morbidity reported.). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of

Study	Wilens 2008 ⁶⁸⁸
	treatment: Not applicable / Not stated / Unclear (Not stated. Response not an exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear (AISRS baseline mean = ~40.3, ASRS baseline mean = 50, CGI-S baseline mean = 4.8).
Indirectness of population	No indirectness
Interventions	<p>(n=72) Intervention 1: CNS stimulants - Atomoxetine. Atomoxetine (25-100 mg daily) for approximately 12 weeks. Treatment was initiated at 25 mg/day at the beginning of the second week and 80 mg at the end of the second week. At any other visit after 4 weeks of treatment, the dose could be increased to 100 mg/day. 80 or 100 mg doses could be administered as a single daily dose or equally divided according to tolerability. Duration 12 weeks. Concurrent medication/care: No other psychopharmacological treatment were permitted during the study other than limited hypnotic use Further details: 1. Dose: Not applicable / Not stated / Unclear (25-100 mg daily). 2. Method of titration: Titrated to optimum dose (Unclear. Appears as if titrated to optimum response and tolerability.).</p> <p>(n=75) Intervention 2: No treatment - Placebo. Placebo to match active treatment. Duration 12 weeks. Concurrent medication/care: No other psychopharmacological treatment were permitted during the study other than limited, intermittent hypnotic use Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration:</p>
Funding	Study funded by industry (study funded Elli Lilly and Company)

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

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Adult: CGI-I at 12 weeks; Group 1: mean 2.9 (SD 1.1); n=32, Group 2: mean 3.4 (SD 1.2); n=48; CGI-I 1-7 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Adult: ADHD Investigator Symptom Rating Scale (AISRS) at 12 weeks; Group 1: mean -13.6 (SD 11.35); n=32, Group 2: mean -8.31 (SD 11.44); n=48; AISRS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome for Adult: Adult ADHD Self-report Scale (ASRS) at 12 weeks; Group 1: mean -12.9 (SD 12.8); n=32, Group 2: mean -8.3 (SD 12.9); n=48; ASRS 0-54? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome for Adult: CGI-S at 12 weeks; Group 1: mean -1 (SD 1.2); n=32, Group 2: mean -0.7 (SD 1.1); n=48; CGI-S 1-7 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Behavioural outcomes at <3- or >6-months

- Actual outcome for Adult: Obsessive Compulsive Drinking Scale (OCDS) at 12 weeks; Group 1: mean -6 (SD 5.5); n=32, Group 2: mean -3.4 (SD 7.04);

Study	Wilens 2008 ⁶⁸⁸
	n=48; OCDS ? Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
	Protocol outcome 4: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Adult: Discontinuation due to adverse events at 12 weeks; Group 1: 7/67, Group 2: 2/73; Risk of bias: High; Indirectness of outcome: No indirectness
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	All outcomes: very high risk of bias, downgraded twice for attrition bias due to (1) over 10% of the data missing overall and (2) a difference of over 10% in missing rates between groups

Study	Wilens 2015 ⁶⁹⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	15 weeks, including 7 week dose titration, 6 week maintenance phase and 2 week taper (n=312)
Countries and setting	Conducted in USA; Setting: Phase 3 trial, multicentre, 48 sites
Line of therapy	1st line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV ADHD determined by K-SADS-PL assessment
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 13-17 with ADHD and ADHDRS-IV score ≥ 32 and CGI-S ≥ 4
Exclusion criteria	Comorbid psychiatric diagnosis except oppositional defiant disorder, cardiac disorder, or any medications that affected the heart or led to sedation.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 14.5 (1.39). Gender (M:F): 103/54. Ethnicity: White 72.8%, African American or black 17.0%, other and mixed 10.2%
Further population details	1. ADHD subtype: All/mixed subtypes (Combined 67.9%, inattentive 29.2%, Hyperactive 2.9%). 2. Age: Young people (13-18 years) 3. At risk population: General population 4. Comorbidities: ODD (Present in 11%). 5. Diagnostic method: DSM 6. Line of treatment: Mixed line (including drug naive) (Around 75%

Study	Wilens 2015 ⁶⁹⁴
	population had previously used stimulant medication). 7. Severity: Mixed
Indirectness of population	No indirectness
Interventions	<p>(n=157) Intervention 1: Guanfacine. Titrated from 1mg up to 4-7mg once daily, depending on weight, over 7 weeks. Duration 15 weeks. Concurrent medication/care: Pts excluded if on medication affecting the heart, blood pressure or with central-nervous-system side-effects. Otherwise could continue medication and psychosocial treatment, as long as held steady during the trial Further details: 1. Dose: 2. Method of titration:</p> <p>(n=155) Intervention 2: No treatment - Placebo. One tablet once a day, increased depending on weight over seven weeks, then maintained for six weeks. Duration 15 weeks. Concurrent medication/care: Pts excluded if on medication affecting the heart, blood pressure or with central-nervous-system side-effects. Otherwise could continue medication and psychosocial treatment, as long as held steady during the trial Further details: 1. Dose: 2. Method of titration:</p>
Funding	Study funded by industry (Phase 3 clinical trial by Shire Development, LLC)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS-IV total at 13 weeks;

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 51, Reason: Adverse events (9), protocol violation (1), participant withdrawal (16), lost to fu (10), lack of efficacy (9), other (6); Group 2 Number missing: 52, Reason: Adverse events (3), protocol violation (3), participant withdrawal (12), lost to fu (3), lack of efficacy (25), other (6)

- Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity/impulsivity subscale at 13 weeks;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 51, Reason: Adverse events (9), protocol violation (1), participant withdrawal (16), lost to fu (10), lack of efficacy (9), other (6); Group 2 Number missing: 52, Reason: Adverse events (3), protocol violation (3), participant withdrawal (12), lost to fu (3), lack of efficacy (25), other (6)

- Actual outcome for Children (up to 18 years): ADHD-RS-IV inattentive subscale at 13 weeks;

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 51, Reason: Adverse events (9), protocol violation (1), participant withdrawal (16), lost to fu (10), lack of efficacy (9), other (6); Group 2 Number missing: 52, Reason: Adverse events (3), protocol violation (3), participant withdrawal (12), lost to fu (3), lack of efficacy (25), other (6)

Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months

Study	Wilens 2015 ⁶⁹⁴
	<p>- Actual outcome for Children (up to 18 years): Early termination (any reason) at 15 weeks; Group 1: 51/157, Group 2: 52/155 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Adverse events (9), protocol violation (1), participant withdrawal (16), lost to fu (10), lack of efficacy (9), other (6); Group 2 Number missing: 3, Reason: Adverse events (3), protocol violation (3), participant withdrawal (12), lost to fu (3), lack of efficacy (25), other (6)</p> <p>- Actual outcome for Children (up to 18 years): Early termination (for adverse event) at 15 weeks; Group 1: 9/157, Group 2: 3/155 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Adverse events (9), protocol violation (1), participant withdrawal (16), lost to fu (10), lack of efficacy (9), other (6); Group 2 Number missing: 3, Reason: Adverse events (3), protocol violation (3), participant withdrawal (12), lost to fu (3), lack of efficacy (25), other (6)</p> <p>Protocol outcome 3: Academic outcomes (literacy and numeracy) at <3- or >6-months - Actual outcome for Children (up to 18 years): WFIRS-P Learning and School (LS) subscale at 13 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 51, Reason: Adverse events (9), protocol violation (1), participant withdrawal (16), lost to fu (10), lack of efficacy (9), other (6); Group 2 Number missing: 52, Reason: Adverse events (3), protocol violation (3), participant withdrawal (12), lost to fu (3), lack of efficacy (25), other (6)</p>
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Emotional dysregulation at <3- or >6-months

Study	Wolraich 2001 ⁷⁰¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=278)
Countries and setting	Conducted in USA; Setting: 14 investigational sites
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Clinical diagnosis
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable

Study	Wolraich 2001 ⁷⁰¹
Inclusion criteria	(1) Clinical diagnosis of ADHD (2) who were taking methylphenidate or had taken it in the past, on a dose of at least 10mg but no more than 60mg
Exclusion criteria	(1) any acute or serious chronic disease (2) hypersensitivity to methylphenidate or were having significant adverse experiences from it, or were taking a medication that would interfere with the safe administration of the drug (3) glaucoma, Tourette's, ongoing seizure disorder, or a psychotic disorder, or girls who had reached menarche. (4) those that had not received methylphenidate in the 4 weeks prior to the study took part in a 4 week open label titration phase to reach their maximum dosage
Recruitment/selection of patients	Through radio and newspaper advertisements
Age, gender and ethnicity	Age - Range: 6 to 12 years. Gender (M:F): 233:49. Ethnicity: 84.4% White, 7.4% Black, 4.3% Other, 3.5% Hispanic and 0.4% Asian
Further population details	1. ADHD subtype: All/mixed subtypes (73.4% combined, 19.5% inattentive and 7.1% hyperactive/impulsive). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Mixed (41.8% ODD, 11.3% conduct disorder, 5.3% tics disorder, 1.4 %anxiety disorders, 0.7% depression). 5. Diagnostic method: Not applicable / Not stated / Unclear 6. Line of treatment: Mixed line (including drug naive) (20.2%received no stimulant therapy, 67.7% methylphenidate, 5.7% other medication, 6.4% hadn't received any medication in the previous 4 weeks). 7. Severity: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=94) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations). Patients were assigned to 1 of 3 treatment dose levels (18mg per day, 36mg per day or 54mg per day) based on either their titration or conversion from previous methylphenidate treatment. 31 were on 18mg, 41 on 36mg and 22 on 54mg. Duration 4 weeks. Concurrent medication/care: Behavioural interventions allowed as long as they had been initiated before the start of the study Further details: 1. Dose: Mixed 2. Method of titration: Mixed</p> <p>(n=95) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations). Participants were assigned to either 5mg t.i.d., 10mg t.i.d., 15mg t.i.d. based on their titration or previous methylphenidate dosage prior to the study. 29 were on 5mg tid, 41 on 10mg t.i.d. and 25 on 15mg t.i.d. Duration 4 weeks. Concurrent medication/care: Behavioural interventions allowed if started before the study Further details: 1. Dose: 2. Method of titration:</p> <p>(n=89) Intervention 3: No treatment - Placebo. Placebo. Duration 4 weeks. Concurrent medication/care: Behavioural interventions allowed if started before the trial Further details: 1. Dose: 2. Method of titration:</p>

Study	Wolraich 2001 ⁷⁰¹
Funding	Study funded by industry (AZLA Corporation)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus IR METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS)</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): SNAP-IV teacher rated inattention subscale at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13 - Actual outcome for Children (up to 18 years): SNAP-IV teacher rated hyperactivity/impulsivity subscale at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13 - Actual outcome for Children (up to 18 years): SNAP-IV parent rated hyperactivity/impulsivity subscale at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13 - Actual outcome for Children (up to 18 years): Treatment response (CGI score of 1 or 2) at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: OROS METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): SNAP-IV teacher rated inattention subscale at 4 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 43 - Actual outcome for Children (up to 18 years): SNAP-IV teacher rated hyperactivity/impulsivity subscale at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13 - Actual outcome for Children (up to 18 years): SNAP-IV parent rated hyperactivity/impulsivity subscale at 4 weeks; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 13 - Actual outcome for Children (up to 18 years): Treatment response (CGI score of 1 or 2) at 4 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 38</p>	

Study	Wolraich 2001 ⁷⁰¹
<p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 4 weeks; Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p> <p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IR METHYLPHENIDATE (INCLUDING MODIFIED-RELEASE PREPARATIONS) versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): SNAP-IV teacher rated inattention subscale at 4 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 38 - Actual outcome for Children (up to 18 years): SNAP-IV parent rated hyperactivity/impulsivity subscale at 4 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 38 - Actual outcome for Children (up to 18 years): Treatment response (CGI score of 1 or 2) at 4 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 38</p> <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Drop out due to adverse events at 4 weeks; Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	Young 2011 ⁷¹⁰ (Wietecha 2012 ⁶⁷⁰)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=502)
Countries and setting	Conducted in USA; Setting: 42 outpatient sites in the US
Line of therapy	Mixed line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline	Adequate method of assessment/diagnosis: DSM-IV

Study (subsidiary papers)	Young 2011 ⁷¹⁰ (Wietecha 2012 ⁶⁷⁰)
condition	
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) DSM-IV-TR criteria for adult ADHD (2) a historical diagnosis during childhood (3) CGI-ADHD-S score of 4+ (4) Required to meet family unit criteria (reciprocal relationship with a person of the opposite sex and living in the same household with at least 1 child between 7 to 17 years old).
Exclusion criteria	(1) Conditions excluded: bipolar, psychotic disorder, current major depression, anxiety disorder, substance abuse (2) those that had previously taken atomoxetine or were taking any psychotropic medication.
Recruitment/selection of patients	From October 2004 to October 2009
Age, gender and ethnicity	Age - Mean (SD): 41.3 (7.2). Gender (M:F): 239/263 . Ethnicity: 84.9% white, 15.1% not specified
Further population details	1. ADHD subtype: All/mixed subtypes (68.7% combined, 31.1% inattentive, 0.2% hyperactive/ impulsive). 2. Age: Adults 18-65 years) (Adults 18 years and over with a child under 17 years). 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: Mixed line (including drug naive) (83.7% of study population were drug naive). 7. Severity: Not applicable / Not stated / Unclear (Mild possibly excluded (CGI-S of 4 or more)).
Extra comments	68.7% of the study population were of the combined subtype of ADHD, 31.1% of inattentive subtype, 0.2% of the hyperactive/ impulsive subtype. No co-morbid condition reported. Participants randomised to the intervention arm were initiated to treatment during an assessment stage prior to the trial. Participants who were unable to tolerate the drug were excluded from the trial.
Indirectness of population	Serious indirectness: 16% have had previous treatment
Interventions	(n=268) Intervention 1: CNS stimulants - Atomoxetine. Two different titrations. 147 had on-label (40mg/d ATX for 3 days followed by 80mg/d). 121 on slow (40mg/d for a week followed by 80mg/d) - discontinued if unable to tolerate. After week 2, the dose was increased to 100mg/d maximum or 60mg/d minimum). If unable to tolerate 60mg/d after week 2, patients were discontinued. Duration 24 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration: (n=234) Intervention 2: No treatment - Placebo. Placebo. Duration 24 weeks. Concurrent medication/care: not stated Further details: 1. Dose: 2. Method of titration:
Funding	Study funded by industry (Lilly USA)

Study (subsidiary papers)	Young 2011 ⁷¹⁰ (Wietecha 2012 ⁶⁷⁰)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE versus PLACEBO	
<p>Protocol outcome 1: ADHD symptoms at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: CAARS total ADHD symptoms score (adjusted) at 24 weeks; Group 1: mean -14.3 (SD 11.8); n=264, Group 2: mean -8.3 (SD 11); n=232; CAARS 0 - 90 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS ADHD symptoms score - inattentive subscale (adjusted) at 24 weeks; Group 1: mean -8.1 (SD 6.9); n=264, Group 2: mean -4.4 (SD 6.4); n=232; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CAARS ADHD symptoms score - hyperactive/impulsivity subscale (adjusted) at 24 weeks; Group 1: mean -6.2 (SD 6); n=264, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: AISRS scale total score (adjusted) at 24 weeks; Group 1: mean -13.7 (SD 12.5); n=264, Group 2: mean -8 (SD 11); n=232; AISRS 0 - 54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: AISRS scale inattentive subscale score (adjusted) at 24 weeks; Group 1: mean -7.6 (SD 7); n=264, Group 2: mean -4.4 (SD 6.3); n=232; AISRS SUBSCALE 0-27 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: AISRS scale hyperactivity subscale score (adjusted) at 24 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: CGI-ADHD-S at 24 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adult: Patients responded (based on 25% decrease from baseline on CAARS) at 24 weeks; Group 1: 180/264, Group 2: 97/232; Risk of bias: ; Indirectness of outcome: No indirectness <p>Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Dropped out due to adverse events at 24 weeks; Group 1: 57/268, Group 2: 22/234; Risk of bias: High; Indirectness of outcome: No indirectness <p>Protocol outcome 3: Emotional dysregulation at <3- or >6-months</p> <ul style="list-style-type: none"> - Actual outcome for Adult: Montgomery-Åsberg Depression Rating Scale total score (adjusted) at 24 weeks; Group 1: mean -0.6 (SD 6.5); n=264, Group 2: mean 0.4 (SD 6.2); n=232; MADRS 0-60 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness 	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months
Risk of bias details	All outcomes: very high risk of bias, downgraded twice for attrition bias due to (1) over 10% of the data missing overall and (2) a difference of over 10% in missing rates between groups, with an attrition rate of over 50% in the experimental group.

Study	Zarinara 2010 ⁷¹¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Iran; Setting: Outpatient clinic and adolescent clinic at Roozbeh Psychiatric Hospital in Tehran, Iran
Line of therapy	Unclear
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR
Stratum	Children (up to 18 years): Children
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects included those that clearly met the DSM-IV-TR diagnostic criteria for ADHD. Total and/or subscale scores on ADHD-RS-IV School version of at least 1.5 standard deviations above norms for patient's age and gender.
Exclusion criteria	History or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders or any current psychiatric comorbidity that required pharmacotherapy, any evidence of suicide risk and intellectual disability. Patients were also excluded if they had a chronic medical condition or hypertension/hypotension.
Recruitment/selection of patients	From the outpatient child and adolescent clinic at Roozbeh Psychiatric Hospital
Age, gender and ethnicity	Age - Range: 6-13 years old. Gender (M:F): 27:11. Ethnicity: 100% Persian
Further population details	1. ADHD subtype: Combined (100% combined). 2. Age: Children (6-12 years) (6-13 years). 3. At risk population: Not applicable / Not stated / Unclear (Not stated). 4. Comorbidities: Not applicable / Not stated / Unclear (Not stated. Psychiatric comorbidities were exclusion criteria). 5. Diagnostic method: DSM (DSM-IV-TR). 6. Line of treatment: Not applicable / Not stated / Unclear (Unclear line. Response not exclusion criteria). 7. Severity: Not applicable / Not stated / Unclear (Baseline ADHD-RS-IV scores were ~ 30 (teacher)).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Other antidepressants - Venlafaxine. Patients were randomised to receive 50-75 mg/day depending on weight. 50 mg per day for <30 kg and 75 mg per day for >30 kg. Titration of drug involved the following schedule: week 1: 25 mg/day, week 2: 50 mg/day (one capsule in the morning and one at midday) and week 3: 75 mg/day for children >30 kg (one capsule in the morning, one at midday and one at 16:00). Duration 6 weeks. Concurrent medication/care: not stated Further details: 1. Dose: Not applicable / Not stated / Unclear (50-75 mg/day). 2. Method of titration: Fixed

Study	Zarinara 2010⁷¹¹
	dose (Dose titrated according to weight). (n=19) Intervention 2: CNS stimulants - Methylphenidate (including modified-release preparations) . Patients were randomised to receive 20-30 mg/day depending on weight.20mg per day for <30 kg and 30mg day for >30 kg. Titration of drug involved the following schedule: week 1: 10 mg/day(5 mg in the morning and 5 mg at mid-day), week 2: 20 mg/ day (10 mg in the morning and 10 mg at mid-day) and week 3:30 mg/day for children >30 kg (10 mg in the morning, 10 mg midday and 10 mg at 16:00). Duration 6 weeks. Concurrent medication/care: not stated Further details: 1. Dose: Not applicable / Not stated / Unclear (20-30 mg/day). 2. Method of titration: Fixed dose (Titrated according to weight).
Funding	Academic or government funding (Grant from Tehran University of Medical Sciences)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VENLAFAXINE versus METHYLPHENIDATE	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome: Parent ADHD Rating Scale at 6 weeks; Group 1: mean -14.15 (SD 7.01); n=18, Group 2: mean -16.63 (SD 8.59); n=18; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome: Teacher ADHD Rating Scale at 6 weeks; Group 1: mean -13.05 (SD 4.77); n=18, Group 2: mean -15.31 (SD 8.13); n=18; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Risk of bias details	Low risk of bias

D.2 Pharmacological sequencing

1 **D.2.1 Pre-School children (under 6 years of age)**

2 No evidence found.

3 **D.2.2 Children and young people (6-18 years old)**

Study	Carlson 2007 ¹³⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=25, n=17 in treatment groups of interest)
Countries and setting	Conducted in USA; Setting: No details provided
Line of therapy	2nd line
Duration of study	Intervention time: 10 weeks (2 phases)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	DSM-IV diagnosis of ADHD (any type), a rating on the ADHD Rating Scale Version IV Parent Reported-Investigator Reported version (ADHDRS-IV-PARENT:Inv) of at least 1.5 standard deviations above age and gender norms; and a severity rating of at least moderate on the Clinical Global Impressions Severity Scale (CGI-S). Previous treatment failure in preceding 12 months: insufficient response to an adequate stimulant trial (inadequate response was determined by the child's prescribing physician)
Exclusion criteria	Children weighing less than 22 kg or more than 60 kg at study entry were excluded. Also children that had any other Axis 1 diagnosis. Presence of comorbid oppositional defiant disorder was not an exclusion criteria. Children who had a history of intolerance or non-response to atomoxetine were excluded. All patients were required to be free of any excluded medications for at least 5 days prior to baseline ratings and randomization.
Recruitment/selection of patients	5 outpatient centres in the US
Age, gender and ethnicity	Age - Mean (SD): 9.6 (1.8) - for 25 who met inclusion criteria . Gender (M:F): 21 (83%) of original 25 who met inclusion criteria were male. . Ethnicity: 83% Caucasian
Further population details	1. ADHD subtype: All/mixed subtypes (19 of 25 had combined subtype). 2. Age: Children (6-12 years) 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear (12 of 25 who met inclusion criteria has oppositional defiant disorder). 5. Diagnostic method: DSM (DSM-IV diagnosis of ADHD). 6. Line of treatment: Mixed line (non-response only, mixed treatment) (None 1st line. All had prior stimulant treatment and those with insufficient response were included.). 7. Severity: Mixed

Study	Carlson 2007¹³⁹
	(Severity of at least moderate on the CGI-S).
Extra comments	Of the 25 who met inclusion criteria: 79% met the criteria for ADHD combined subtype, 50% comorbid with oppositional defiant disorder.
Indirectness of population	No indirectness
Interventions	<p>(n=9) Intervention 1: CNS stimulants - Methylphenidate (including modified-release preparations) . Titrated to target dose of 1.08 mg/kg/day with a maximum of 1.2 mg/kg/day. 6 week trial. . Duration 6 week trial on OROS methylphenidate. 4 weeks previously on atomoxetine and placebo, atomoxetine sustained during OROS methylphenidate trial. Concurrent medication/care: All children received an open label 4 week trial of atomoxetine and placebo. Doses were titrated to target dose of 1.2 mg/kg/day, with a maximum of 1.4 mg/kg/day. Patients/investigators were unaware of when active augmentation would start. After 4 weeks, patients with improved symptoms remained on atomoxetine and placebo (n=4). Patients with no improvements were randomly assigned to methylphenidate or placebo. All patients were required to be free of any excluded medications for at least 5 days prior to baseline ratings and randomisation. Further details: 1. Dose: Moderate (Titrated to target dose of 1.08 mg/kg/day with a maximum of 1.2 mg/kg/day). 2. Method of titration: Titrated to optimum dose (Titrated to target dose of 1.08 mg/kg/day with a maximum of 1.2 mg/kg/day).</p> <p>(n=8) Intervention 2: No treatment - Placebo. No details. Duration 6 week trial on placebo. 4 weeks previously on atomoxetine and placebo, atomoxetine sustained during placebo trial. . Concurrent medication/care: All children received an open label 4 week trial of atomoxetine and placebo. Doses were titrated to target dose of 1.2 mg/kg/day, with a maximum of 1.4 mg/kg/day. Patients/investigators were unaware of when active augmentation would start. After 4 weeks, patients with improved symptoms remained on atomoxetine and placebo (n=4). Patients with no improvements were randomly assigned to methylphenidate or placebo. All patients were required to be free of any excluded medications for at least 5 days prior to baseline ratings and randomisation. Further details: 1. Dose: Not applicable / Not stated / Unclear (Placebo). 2. Method of titration: Not applicable / Not stated / Unclear (Not stated if titration was imitated in placebo group).</p>
Funding	Study funded by industry (Eli Lilly)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATOMOXETINE/ PLACEBO THEN METHYLPHENIDATE versus ATOMOXETINE/PLACEBO THEN PLACEBO

Protocol outcome 1: Serious adverse events at All

- Actual outcome for Children (up to 18 years): Adverse events leading to hospitalisation/death/disability at 10 weeks; Group 1: 0/9, Group 2: 0/7; Risk of

Study	Carlson 2007¹³⁹
bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 2: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinuation of treatment due to TEAEs at After 6 week trial of MPH vs placebo (phase 2); Group 1: 1/9, Group 2: 1/12; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; ADHD symptoms at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	NCT00734578 trial: Cutler 2014¹⁹⁷ (Wilens 2012⁶⁹⁰)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=461. 455 received study drug.)
Countries and setting	Conducted in USA; Setting: Multicentre (59 US sites)
Line of therapy	Unclear
Duration of study	Intervention + follow up: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children and adolescents 6-17 years of age with a primary diagnosis of ADHD exhibiting partial but suboptimal response to a stable (>4 weeks) dose of a long acting oral psychostimulant. Suboptimal response was defined as symptom improvement in the opinion of the investigator yet persistence of mild-to-moderate ADHD symptoms of any subtype, based on a detailed psychiatric evaluation using the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL). Subjects were required to have exhibited partial but suboptimal response to treatment with a long-acting oral psychostimulant for > 4 weeks prior to screening. A suboptimal response was documented at least 14 days before the baseline visit and confirmed at the baseline visit. Suboptimal response was defined as treatment with a stable dose of psychostimulant for >4 weeks with improvement in, yet persistence of, mild to moderate ADHD symptoms (ADHD -RS-IV total score >24 and CGI> 3) as well as investigator judgement.
Exclusion criteria	Patients with a current, controlled or uncontrolled comorbid, psychiatric diagnosis (except ODD), including

Study (subsidiary papers)	NCT00734578 trial: Cutler 2014¹⁹⁷ (Wilens 2012⁶⁹⁰)
	any severe comorbid disorders, a history or presence cardiac abnormality and as well as participants who did not demonstrate a response to their current stimulant medication
Recruitment/selection of patients	Patients from 59 US sites from September 2008 through December 2009
Age, gender and ethnicity	Age - Range: 6-17 years. Gender (M:F): 326/129. Ethnicity: 67.7% white, 32.3% other
Further population details	1. ADHD subtype: All/mixed subtypes (All subtypes included). 2. Age: 3. At risk population: 4. Comorbidities: 5. Diagnostic method: 6. Line of treatment: 7. Severity:
Indirectness of population	Serious indirectness: Patients who did not demonstrate a response to their current stimulant were excluded.
Interventions	<p>(n=154) Intervention 1: Guanfacine. At baseline, subjects were randomised in a 1:1:1 ratio (stratified by psychostimulant type) to receive guanfacine (GXR) on awakening and placebo at bedtime (GXR AM). 9 week treatment included dose optimisation (5 weeks), dose maintenance (3 weeks) and dose tapering (1 week). Duration 9 weeks. Concurrent medication/care: Subjects continued to take their stable morning psychostimulant dose in addition to their morning or evening dose of GXR or placebo Further details: 1. Dose: High (Mean (SD) 3.3 (1) mg/day). 2. Method of titration: Titrated to optimum dose</p> <p>(n=153) Intervention 2: Guanfacine. At baseline, subjects were randomised in a 1:1:1 ratio to receive placebo on awakening and GXR at bedtime (GXR PM). 9 week treatment included dose optimisation (5 weeks), dose maintenance (3 weeks) and dose tapering (1 week). Duration 9 weeks. Concurrent medication/care: Subjects continued to take their stable morning psychostimulant dose in addition to their morning or evening dose of GXR or placebo Further details: 1. Dose: High (Mean (SD) 3.2 (1) mg/day). 2. Method of titration: Titrated to optimum dose</p> <p>(n=154) Intervention 3: No treatment - Placebo. At baseline, subjects were randomised in a 1:1:1 ratio to receive placebo at both morning and bedtime in addition to their current psychostimulant dose. 9 week treatment included dose optimisation (5 weeks), dose maintenance (3 weeks) and dose tapering (1 week). Duration 9 weeks. Concurrent medication/care: subjects continued to take their stable morning psychostimulant dose in addition to their morning or evening dose of GXR or placebo Further details: 1. Dose: Not applicable / Not stated / Unclear (Placebo). 2. Method of titration: Not applicable / Not stated / Unclear (Unclear).</p>
Funding	Study funded by industry (Clinical research was funded by Shire Development LLC. Shire provided funding to SCI and MedErgy for supporting and editing the clinical papers.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GXR AM versus PLACEBO	
Protocol outcome 1: CGI at <3- or >6-months	

Study (subsidiary papers)

NCT00734578 trial: Cutler 2014¹⁹⁷ (Wilens 2012⁶⁹⁰)

- Actual outcome for Children (up to 18 years): CGI-I improved or much improved or very much improved at 8 weeks; Group 1: 105/149, Group 2: 88/152; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS-IV: placebo adjusted LS mean reduction at 8 weeks; MD -4.5 (95%CI -7.5 to -1.4); Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS-IV inattention subscale: placebo adjusted LS mean reduction at 8 weeks; MD -2.4 (95%CI -3.9 to -0.9); Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity/impulsivity subscale: placebo adjusted LS mean reduction at 8 weeks; MD -2.1 (95%CI -3.4 to -0.7); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Early discontinuation of treatment due to adverse events at 9 weeks; Group 1: 4/150, Group 2: 1/154; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): Severe TEAEs at 9 weeks; Group 1: 3/150, Group 2: 1/153; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GXR PM versus PLACEBO

Protocol outcome 1: CGI at <3- or >6-months

- Actual outcome for Children (up to 18 years): CGI-I improved or much improved or very much improved at 8 weeks; Group 1: 110/148, Group 2: 88/152; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-RS-IV: placebo adjusted LS mean reduction at 8 weeks; MD -5.3 (95%CI -8.3 to -2.3); Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS-IV inattention subscale: placebo adjusted LS mean reduction at 8 weeks; MD -3.1 (95%CI -4.6 to -1.5); Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity/impulsivity subscale: placebo adjusted LS mean reduction at 8 weeks; MD -2.3 (95%CI -3.6 to -0.9); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months

- Actual outcome for Children (up to 18 years): Severe TEAEs at 9 weeks; Group 1: 10/152, Group 2: 1/153; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Children (up to 18 years): Early discontinuation of treatment due to adverse events at 9 weeks; Group 1: 6/152, Group 2: 1/153; Risk of bias: High; Indirectness of outcome: No indirectness

Study (subsidiary papers)	NCT00734578 trial: Cutler 2014¹⁹⁷ (Wilens 2012⁶⁹⁰)
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Adverse events leading to hospitalisation/death/disability at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study (subsidiary papers)	NCT01106430 trial: Dittmann 2014²⁰⁶ (Nagy 2015⁴⁶⁹, Dittmann 2013²⁰⁷)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=267)
Countries and setting	Conducted in Belgium, Canada, Germany, Hungary, Italy, Poland, Spain, Sweden, USA; Setting: 51 sites in 9 countries including Canada, USA, and seven European countries: Belgium, Germany, Hungary, Italy, Poland, Spain, Sweden
Line of therapy	Unclear
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ADHD-RS-IV total score of 28 or higher at baseline, and an inadequate response to previous or current MPH treatment
Exclusion criteria	Intolerable adverse events from previous MPH treatment, previous exposure to amphetamine or ATX, previous treatment with more than one MPH medication, failure to respond to more than one previous course of MPH medication and good control of ADHD symptoms. Comorbid psychiatric diagnosis, conduct disorder, suicide risk, weight below 22.7 kg, suspected substance abuse and history of seizures
Recruitment/selection of patients	Study was conducted between June 2010 to July 2012 at the 51 centres in 9 countries
Age, gender and ethnicity	Age - Range: 6 - 17 years. Gender (M:F): 197:70. Ethnicity: 80% Hispanic, 20% other
Further population details	1. ADHD subtype: All/mixed subtypes (78.3% of the patients were classified as the combined ADHD subtype, 3.4% as the predominantly hyperactive-impulsive and 16.5% as the predominantly inattentive). 2. Age: Mixed (People aged 6-17 years old). 3. At risk population: Not applicable / Not stated / Unclear 4. Comorbidities: Not applicable / Not stated / Unclear (Comorbid psychiatric diagnosis, conduct disorder, suicide risk, suspected substance abuse and history of seizures excluded.). 5. Diagnostic method: DSM (Satisfied DSM 4th edition criteria for a primary diagnosis of ADHD). 6. Line of treatment: 2nd line (non-

Study (subsidiary papers)	NCT01106430 trial: Dittmann 2014²⁰⁶ (Nagy 2015⁴⁶⁹, Dittmann 2013²⁰⁷)
	response to CNS stimulants) (Non response to a trial of methylphenidate). 7. Severity: Mixed (Diagnosis of at least moderate severity. ADHD-RS-IV score of 28 or higher.).
Extra comments	78.3% of the patients were classified as the combined ADHD subtype, 3.4% as the predominantly hyperactive-impulsive and 16.5% as the predominantly inattentive.
Indirectness of population	No indirectness
Interventions	<p>(n=133) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Once daily, morning dose at 7 am (+/- 2 hrs). LDX was initially provided in a single capsule of 30, 50 or 70 mg, with patients starting at 30mg/day. 4 week dose optimization (weekly increases of 20mg/day if needed) and 5 weeks of dose maintenance. Optimization phase involved adjustment until and 'acceptable' response was achieved. This was defined as a reduction of at least 30% from baseline ADHD-RS-IV score and a CGI-I score of 1 or 2 with tolerable side effects.</p> <p>. Duration 9 weeks. Concurrent medication/care: Patients were required to discontinue any psychoactive medication for a 7 day washout period prior to baseline</p> <p>Further details: 1. Dose: High (30 or 50 or 70 mg. Mean (SD) dose from visit 4 was 52.5 (16) mg/day). 2. Method of titration: Titrated to optimum dose (Optimization phase involved adjustment until and 'acceptable' response was achieved. This was defined as a reduction of at least 30% from baseline ADHD-RS-IV score and a CGI-I score of 1 or 2 with tolerable side effects.).</p> <p>Comments: Patients to who were unable to tolerate the study drug were withdrawn from the study.</p> <p>(n=134) Intervention 2: CNS stimulants - Atomoxetine. ATX was available in 10-, 18-,25-, 49- and 60- mg capsules. Patients weighing less than 70kg were started on 0.5mg/kg/day (not exceeding 1.4), and patients weighing more than this received 40mg/day, being titrated to 80mg/day and 100mg/day if required. 4 week dose optimization and 5 weeks of dose maintenance. Drugs taken daily at 7am +/- 2 hours. Optimization phase involved adjustment until and 'acceptable' response was achieved. This was defined as a reduction of at least 30% from baseline ADHD-RS-IV score and a CGI-I score of 1 or 2 with tolerable side effects. .</p> <p>Duration 9 weeks. Concurrent medication/care: Patients were required to discontinue any psychoactive medication for a 7 day washout period prior to baseline</p> <p>Further details: 1. Dose: Moderate (Started at 0.5 mg/kg to a maximum of 1.4 mg/kg. Mean (SD) dose from visit 4 was 40.2 (20) mg/day for patients weighing <70kg and 1.2 mg/kg/day for patients >/=70kg.). 2. Method of titration: Titrated to optimum dose (Optimization phase involved adjustment until and 'acceptable' response was achieved. This was defined as a reduction of at least 30% from baseline ADHD-RS-IV score and a CGI-I score of 1 or 2 with tolerable side effects.).</p> <p>Comments: Patients to who were unable to tolerate the study drug were withdrawn from the study.</p>
Funding	Study funded by industry (Shire)

Study (subsidiary papers)	NCT01106430 trial: Dittmann 2014²⁰⁶ (Nagy 2015⁴⁶⁹, Dittmann 2013²⁰⁷)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LDX GROUP versus ATX GROUP</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI improvement of at least one category at Baseline to 9 weeks; Group 1: 90/95, Group 2: 84/97; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV change score (investigator rated) at Baseline to 9 weeks; Group 1: mean -26.3 (SD 11.94); n=100, Group 2: mean -19.4 (SD 12.82); n=101; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV inattentiveness subscale LS mean change. LDX - ATX. (investigator rated) at Baseline to 9 weeks; MD -3.4 (95%CI -4.9 to -1.8); Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity/impulsivity subscale LS mean change. LDX - ATX. (investigator rated) at Baseline to 9 weeks; MD -3.2 (95%CI -4.6 to -1.7); Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Behavioural outcomes at <3- or >6-months - Actual outcome for Children (up to 18 years): Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P) - LS mean change at Baseline to endpoint; Group 1: mean -0.35 (SD 0.3652); n=107, Group 2: mean -0.27 (SD 0.3234); n=113; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Adverse events leading to hospitalisation/death/disability events at All - Actual outcome for Children (up to 18 years): Serious TEAE at Within 9 week treatment period. All patients received at least one dose of study drug. ; Group 1: 0/128, Group 2: 0/134; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinued treatment due to adverse event at Within 9 week treatment period. All patients received at least one dose of study drug. ; Group 1: 8/128, Group 2: 10/134; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months
Study	Gadow 2014²⁵⁶
Study type	RCT (Patient randomised; Parallel)

Study	Gadow 2014 ²⁵⁶
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in USA; Setting: 4 sites in USA.
Line of therapy	2nd line
Duration of study	Intervention time: 9 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ADHD via DSM-IV criteria. Plus evidence of serious physical aggression and severe disruptive behaviour and ODD or CD.
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Evidence of serious physical aggression as defined by parent report to a blinded clinician of a level 3 or greater on Overt Aggression Scale-M of assault against objects, others or self and severe disruptive behaviour defined as equal or above of the 90th percentile using the NCBRF D total and co-occurring ODD or CD.
Exclusion criteria	Full scale IQ<70, pregnancy, medical consideration (seizures, abnormal liver function, first degree family history of type 2 diabetes), lifetime history of pervasive developmental disorder, psychotic disorder, eating disorder, substance abuse disorder, current major depressive disorder, bipolar disorder, attempted suicide, evidence of child abuse.
Recruitment/selection of patients	Parents/guardians signed consent forms and study participants gave consent.
Age, gender and ethnicity	Age - Mean (SD): 8.9 (2). Gender (M:F): Male 77%, Female 23% . Ethnicity: 53% white/Caucasian/European geographic ancestry
Further population details	1. ADHD subtype: All/mixed subtypes (Any subtype of ADHD). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear (Mix of ODD (74%) and CD (26%)). 5. Diagnostic method: DSM (DSM-IV). 6. Line of treatment: 2nd line (non-response only, mixed treatment) (Children who did not show sufficient clinical response to OROS methylphenidate. A second treatment was added.). 7. Severity: Mixed (A rating of at least moderately ill by a blinded clinician. Severity score >=4 CGI.).
Extra comments	Randomisation stratified by site and balanced by ODD and CD
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Antipsychotics - Risperidone. Medication adjusted to achieve optimal therapeutic response. Participant assessments conducted by blinded evaluator without knowledge of treatment or adverse events. Mean dose was 1.7 +/- 0.6 mg/day at week 9. Treatment given in the morning or evening. . Duration 6 weeks. Concurrent medication/care: Methylphenidate dose was 46 +/- 17 mg/day at week 9. Treatment given in the morning. Parents given parent training in child behaviour management techniques

Study	Gadow 2014²⁵⁶
	<p>throughout 9 week intervention period. Further details: 1. Dose: High (Mean dose was 1.7 +/- 0.6 mg/day). 2. Method of titration: Titrated to optimum dose (Adjusted to achieve an optimal therapeutic response).</p> <p>(n=84) Intervention 2: No treatment - Placebo. Medication adjusted to achieve optimal therapeutic response. Participant assessments conducted by blinded evaluator without knowledge of treatment or adverse events. Mean dose was 1.9 +/- 0.7 mg/day at week 9. Treatment given in the morning or evening. . Duration 6 weeks. Concurrent medication/care: Methylphenidate dose was 45 +/- 15 mg/day at week 9. Treatment given in the morning. Parents given parent training in child behaviour management techniques throughout 9 week intervention period. Further details: 1. Dose: Not applicable / Not stated / Unclear (Placebo. 1.9 +/- 0.7 mg/day). 2. Method of titration: Titrated to optimum dose (Adjusted to achieve an optimal therapeutic response).</p>
Funding	Academic or government funding (Study supported by grants from National Institute of Mental Health (NIMH), Case Western Reserve University, University of Pittsburgh, SUNY Stony Brook. Project supported by National Institutes of Health General Clinical Research Center grant, Clinical and Translational Science Awards, National Center for Advancing Translational Sciences grants.)

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

Protocol outcome 1: ADHD symptoms at <3- or >6-months

- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Score (parent rating) at 6 weeks (9th week of complete study); Group 1: mean 0.8 (SD 0.5); n=66, Group 2: mean 1 (SD 0.7); n=71; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Score (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.6 (SD 0.5); n=38, Group 2: mean 0.8 (SD 0.6); n=48; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Attention (parent rating) at 6 weeks (9th week of complete study); Group 1: mean 0.9 (SD 0.6); n=66, Group 2: mean 1.1 (SD 0.7); n=71; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Impulsivity (parent rating) at 6 weeks (9th week of complete study); Group 1: mean 0.8 (SD 0.7); n=66, Group 2: mean 1.1 (SD 0.9); n=71; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Impulsivity (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.5 (SD 0.6); n=38, Group 2: mean 0.7 (SD 0.8); n=48; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Inattention (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.8 (SD 0.6); n=38, Group 2: mean 1 (SD 0.7); n=48; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Hyperactivity (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.5 (SD 0.6); n=38, Group 2: mean 0.4 (SD 0.5); n=48; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children (up to 18 years): ADHD-SC4 Severity Subscore: Hyperactivity (parent rating) at 6 weeks (9th week of complete study);

Study	Gadow 2014 ²⁵⁶
Group 1: mean 0.6 (SD 0.6); n=66, Group 2: mean 0.8 (SD 0.8); n=71; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcome 2: Behavioural outcomes at <3- or >6-months	
- Actual outcome for Children (up to 18 years): ODD DSM-IV (parent rating) at 6 weeks (9th week of complete study); Group 1: mean 0.8 (SD 0.6); n=66, Group 2: mean 1.1 (SD 0.8); n=71; Risk of bias: Low; Indirectness of outcome: No indirectness	
- Actual outcome for Children (up to 18 years): ODD DSM-IV (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.4 (SD 0.6); n=38, Group 2: mean 0.4 (SD 0.6); n=48; Risk of bias: High; Indirectness of outcome: No indirectness	
- Actual outcome for Children (up to 18 years): Peer Conflict Scale (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.2 (SD 0.4); n=38, Group 2: mean 0.2 (SD 0.3); n=48; Risk of bias: High; Indirectness of outcome: No indirectness	
- Actual outcome for Children (up to 18 years): Peer Conflict Scale (parent rating) at 6 weeks (9th week of complete study); Group 1: mean 0.3 (SD 0.4); n=66, Group 2: mean 0.6 (SD 0.7); n=71; Risk of bias: Low; Indirectness of outcome: No indirectness	
- Actual outcome for Children (up to 18 years): CD DSM-IV (parent rating) at 6 weeks (9th week of complete study); Group 1: mean 0.1 (SD 0.2); n=73, Group 2: mean 0.2 (SD 0.2); n=77; Risk of bias: Low; Indirectness of outcome: No indirectness	
- Actual outcome for Children (up to 18 years): CD DSM-IV (teacher rating) at 6 weeks (9th week of complete study); Group 1: mean 0.1 (SD 0.3); n=30, Group 2: mean 0.1 (SD 0.2); n=39; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Adverse events leading to hospitalisation/death/disability at All; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Jain 2011 ³⁴⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in USA; Setting: 40 study sites across USA
Line of therapy	2nd line
Duration of study	Intervention time: 4 weeks intervention plus 1 week screening and 1 week washout period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: DSM-IV-TR criteria
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged 6-12 years old. Met DSM-IV-TR criteria for ADHD. Had ADHD-RS-IV score of ≥ 28 at

Study	Jain 2011³⁴⁸
	baseline after washout. Prior ADHD treatment was discontinued before washout period. Non-remitters to methylphenidate treatment.
Exclusion criteria	None detailed
Recruitment/selection of patients	Subgroup of larger study
Age, gender and ethnicity	Age - Mean (SD): 9 years old. Gender (M:F): 15 (58%) Male, 11 (42%) female. Ethnicity: Not reported
Further population details	1. ADHD subtype: All/mixed subtypes (Subtype not specified). 2. Age: Children (6-12 years) 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear (Comorbidities not specified). 5. Diagnostic method: DSM (DSM-IV-TR criteria). 6. Line of treatment: 2nd line (non-response to CNS stimulants) (Non-remitter to methylphenidate treatment). 7. Severity: Mixed (ADHD-RS \geq 28).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: CNS stimulants - Lisdexamfetamine dimesylate. Randomised equally to either 30 mg/day for 4 weeks, 30 mg/day for week 1 and 50 mg/day for weeks 2-4, 30 mg/day for week 1 and 50 mg/day for week 2 and 70 mg/day for weeks 3-4. Duration 4 weeks. Concurrent medication/care: 1 week washout period before LDX treatment. Further details: 1. Dose: Mixed (Varied dose from 30 mg/day to 70 mg/day depending on randomisation). 2. Method of titration: Fixed dose (Varied dose from 30 mg/day to 70 mg/day depending on randomisation). (n=7) Intervention 2: No treatment - Placebo. Placebo for 4 weeks. Duration 4 weeks. Concurrent medication/care: 1 week washout period before LDX treatment. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Fixed dose
Funding	Study funded by industry (Funded by Shire Canada Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LISDEXAMFETAMINE DIMESYLATE versus PLACEBO	
Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): Clinical response: \geq 30% reduction in ADHD-RS-IV total score and CGI-I of 1 or 2 at 4 weeks; Group 1: 15/19, Group 2: 3/7; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcome 2: Serious adverse events at All - Actual outcome for Children (up to 18 years): Adverse events leading to hospitalisation/death/disability at 4 weeks; Group 1: 0/19, Group 2: 0/7; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; CGI at <3- or >6-months; Behavioural outcomes at <3- or >6-months;

Study	Jain 2011³⁴⁸
study	Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Study	Kollins 2011³⁷⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=198)
Countries and setting	Conducted in USA; Setting: 22 centres in USA
Line of therapy	2nd line
Duration of study	Intervention time: 8 weeks. Dose reduced after week 5.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
Stratum	Children (up to 18 years)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6-17 years old. Hyperactive or combined ADHD subtype. Stable regimen of stimulant treatment (methylphenidate or amphetamine). Stimulant treatment was inadequate: total score of \geq 26 on ADHD-RS-IV after 4 weeks of stimulant treatment. Other inclusion criteria were intelligence quotient \geq 80 and BMI \geq 5th percentile for patient's age and gender.
Exclusion criteria	Current diagnosis or history of psychiatric disorder, sever co-morbid Axis I or Axis II disorder, history of conduct disorder, history of syncopal episodes or seizures, current or past drug abuse, history of clonidine intolerance, use of investigational drug within 30 days of study initiation. Significant illness or abnormality that would increase safety risk of clonidine, clinically significant electrocardiogram readings. Females of childbearing age who were pregnant or lactating or refused birth control. Concomitant use of antihypertensive medications, psychotropic drugs, oral corticosteroids, sedating antihistamines, antidiabetic medications, diet aids and bronchodilators > 3 days per week.
Age, gender and ethnicity	Age - Mean (SD): Placebo group: 10.5 (2.5), Clonidine group: 10.4 (2.5). Gender (M:F): 145 male, 52 female. Ethnicity: Race: 54% white, 27% black, 11% Hispanic, 8% other
Further population details	1. ADHD subtype: All/mixed subtypes (Hyperactive or combined ADHD subtype). 2. Age: Mixed (6-17 years old). 3. At risk population: General population 4. Comorbidities: Not applicable / Not stated / Unclear 5. Diagnostic method: DSM (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.). 6. Line of treatment: Mixed line (non-response only, mixed treatment) 7. Severity: Mixed (Mean ADHD-RS-IV score was 39 for stimulant group and 38.9 for clonidine group).

Study	Kollins 2011 ³⁷⁷
Indirectness of population	No indirectness
Interventions	<p>(n=102) Intervention 1: Clonidine. 0.1 - 0.4 mg/day. Patients started at 0.1 mg/day and dose could be increased by 0.1 mg per week until maximum does achieved. . Duration 8 weeks though reduced dose after 5 weeks. Concurrent medication/care: 58% patients were on methylphenidate and 42% on amphetamines. Further details: 1. Dose: Mixed (0.1 - 0.4 mg/day). 2. Method of titration: Titrated to optimum dose (Clonidine could be increased to reach a maximum dose).</p> <p>(n=96) Intervention 2: No treatment - Placebo. Placebo. Duration 8 weeks. Concurrent medication/care: 62% patients were on methylphenidate and 38% on amphetamines. Further details: 1. Dose: Not applicable / Not stated / Unclear 2. Method of titration: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Study supported by Adrenex Pharmaceuticals, a Shionogi company. Medical writing assistance provided by MedThink ShiCom Inc. Dr Nicole Foreman and Dr Chao Wang (of Shionogi Inc) assisted in analysis and reviewed manuscript.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO</p> <p>Protocol outcome 1: CGI at <3- or >6-months - Actual outcome for Children (up to 18 years): CGI-I at baseline to week 5; Group 1: mean 2.5 (SD 1.2); n=102, Group 2: mean 3 (SD 1.2); n=95; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: ADHD symptoms at <3- or >6-months - Actual outcome for Children (up to 18 years): ADHD-RS-IV improvement at baseline to week 5; Group 1: mean -15.7 (SD 12.3); n=102, Group 2: mean -11.5 (SD 12.2); n=95; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV inattention subscale improvement at baseline to week 5; Group 1: mean -7.8 (SD 6.8); n=102, Group 2: mean -5.8 (SD 6.8); n=95; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children (up to 18 years): ADHD-RS-IV hyperactivity/impulsivity subscale improvement at baseline to week 5; Group 1: mean -7.9 (SD 6.7); n=102, Group 2: mean -5.8 (SD 6.3); n=95; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Dropped out due to adverse events at <3- or >6-months - Actual outcome for Children (up to 18 years): Discontinued treatment due to TEAE at baseline to week 8; Group 1: 1/102, Group 2: 3/96; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Serious adverse events at All; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and

Study	Kollins 2011³⁷⁷
study	numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

1 **D.2.3 Adults**

Study	Butterfield 2016¹³⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in USA; Setting: Conducted at the Rochester Center for Behavioural Medicine (RCBM). In Detroit, USA.
Line of therapy	2nd line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis derived from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Assessed by psychiatric intake.
Stratum	Adult
Subgroup analysis within study	Not applicable
Inclusion criteria	Current ADHD diagnosis. On current treatment of stimulant medications at the time of the screening interview. Had ADHD pharmacological treatment for multiple years. There was a sub-optimal response to current treatment. This was defined as participant's dissatisfaction to clinical progress, a visit 1 baseline score of ≥ 28 by ADHD-RS or CGI-RS of ≥ 4 .
Exclusion criteria	Severe comorbid psychiatric diagnoses, history of psychosis, pervasive developmental disorders, severe Axis II disorders, severe substance dependence. History of hyperthyroidism, hypertension, resting blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, affiliation with study team, receiving unregulated medication, participated in a clinical trial within 30 days, weight less than 30kg or more than 120kg.
Recruitment/selection of patients	Recruited from local advertisements and the clinic's existing patient population.
Age, gender and ethnicity	Age - Mean (SD): 37.54 (12.22). Gender (M:F): 12/14. Ethnicity: 85.6% Caucasian, 11.5 African-American, 3.8% Other
Further population details	1. ADHD subtype: All/mixed subtypes (All participants had ADHD diagnosis using diagnostic criteria for adult ADHD (inattentive, hyperactive/impulsive, combined subtypes)). 2. Age: Adults 18-65 years (Age 19-62.). 3. At risk population: General population (Recruited from local advertisements and the clinic's existing patient population.). 4. Comorbidities: Not applicable / Not stated / Unclear (Excluded people with Axis 1 disorders, severe Axis 2 disorders, severe substance dependence.). 5. Diagnostic method: DSM (Diagnostic and Statistical Manual of Mental Health Disorders (4th edition)). 6. Line of treatment: Not applicable / Not stated / Unclear (Not first line therapy. Sub-optimal response to various ADHD medications). 7. Severity: Not

Study	Butterfield 2016 ¹³⁴
	applicable / Not stated / Unclear (Baseline score of ≥ 28 by ADHD-RS or CGI-RS of ≥ 4).
Indirectness of population	No indirectness
Interventions	<p>(n=13) Intervention 1: Guanfacine. 1mg on second visit and then titrated to optimum dose based on response and tolerance. Doses available were 1mg, 2mg, 3mg, 4mg. A 2 week down titration was begun on visit 9. . Duration 10 weeks. Concurrent medication/care: Stimulant medication previously taken by all participants was continued throughout the study. These medications included lisdexamfetamine, mixed salts, methylphenidate. Further details: 1. Dose: Mixed (1mg on second visit and then titrated to optimum dose based on response and tolerance). 2. Method of titration: Titrated to optimum dose</p> <p>(n=13) Intervention 2: No treatment - Placebo. Placebo matched to guanfacine hydrochloride. Duration 10 weeks. Concurrent medication/care: Stimulant medication previously taken by all participants was continued throughout the study. These medications included lisdexamfetamine, mixed salts, methylphenidate. Further details: 1. Dose: Not applicable / Not stated / Unclear (Unclear if dose was altered). 2. Method of titration: Not applicable / Not stated / Unclear (Unclear if imitation titration took place).</p>
Funding	Academic or government funding (Study sponsorship by Shire.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GUANFACINE versus PLACEBO</p> <p>Protocol outcome 1: ADHD symptoms at <3- or >6-months - Actual outcome for Adult: ADHD-RS at 9 weeks; Group 1: mean 11.85 (SD 7.62); n=13, Group 2: mean 10.92 (SD 8.9); n=13; ADHD-RS 0-54 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at <3- or >6-months; Behavioural outcomes at <3- or >6-months; Dropped out due to adverse events at <3- or >6-months; Risky behaviour at <3- or >6-months; Employment at >6-months; Academic outcomes (literacy and numeracy) at <3- or >6-months; Emotional dysregulation at <3- or >6-months

Appendix E: Forest plots

E.1 Pharmacological efficacy

E.1.1 Children under the age of 5

Methylphenidate versus placebo

Figure 3: ADHD total symptoms parent/ teacher rated at 4 weeks (SNAP-IV parent-teacher composite scores of ≤ 1)

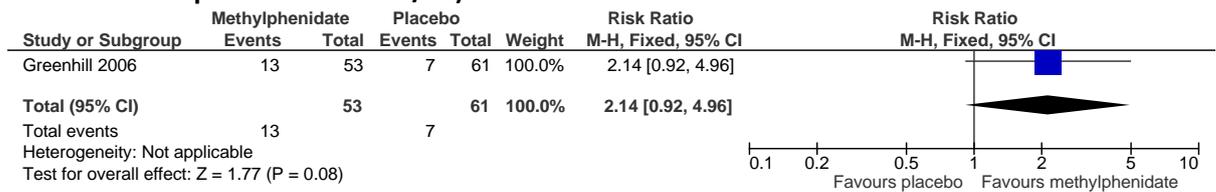


Figure 4: ADHD total symptoms parent rated at 4 weeks; Conners' Parent Rating Scale DSM-IV ADHD subscale; 0-54; lower values are beneficial

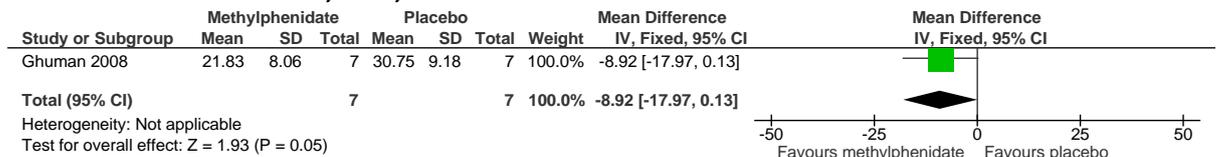
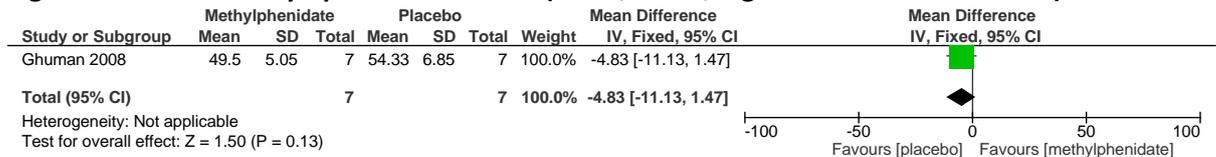


Figure 5: Behaviour symptoms at 4 weeks (CGAS; 0-100; higher values are beneficial)



1 **Risperidone versus methylphenidate**

Figure 6: ADHD total symptoms at 6 weeks (ADHD-RS total scores) parent rated; 0-54, Lower values are beneficial, final values reported

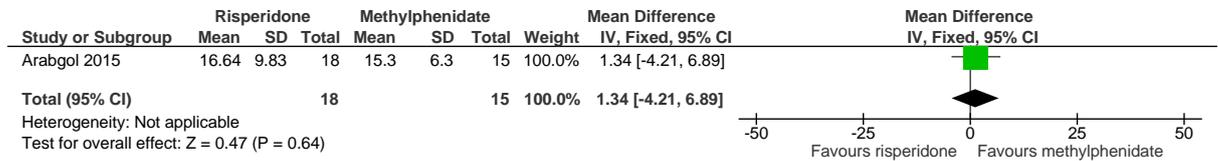
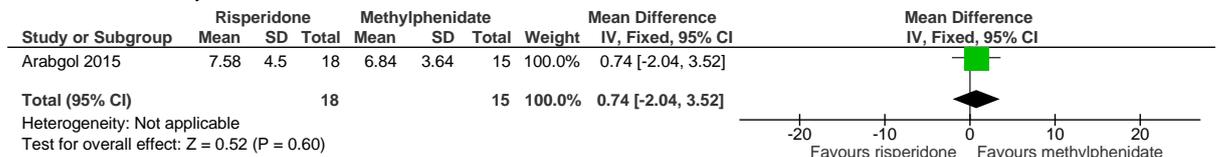
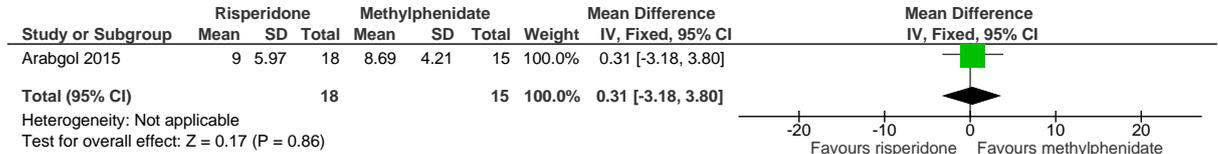


Figure 7: ADHD inattention symptoms at 6 weeks (ADHD-RS inattentive subscale) parent rated; 0-27, Lower values are beneficial



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Figure 8: ADHD hyperactivity symptoms at 6 weeks (ADHD-RS hyperactive subscale) parent rated; 0-27, lower values are beneficial



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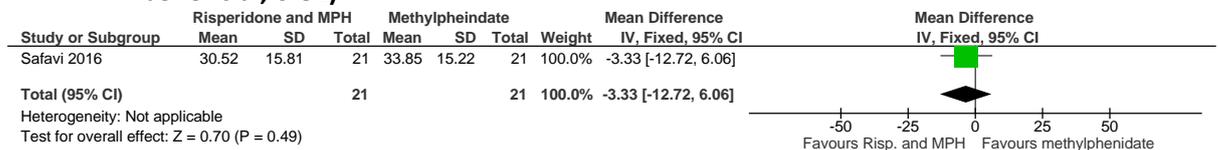
Figure 9: Discontinuation due to adverse events at 6 weeks



4

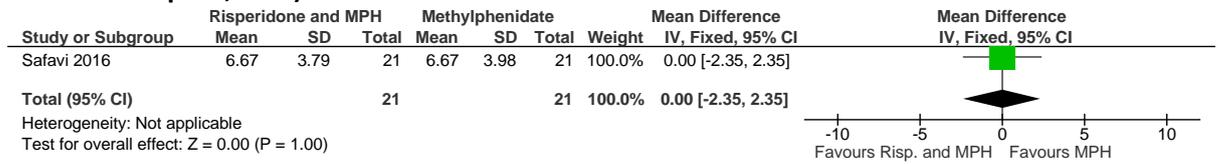
Risperidone and methylphenidate versus methylphenidate

Figure 10: ADHD total symptoms (6 weeks PT; parent rated; CPRS total scores, low scores are beneficial, 0-81)



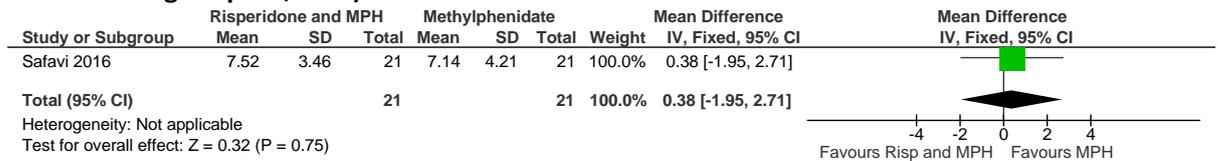
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Figure 11: ADHD inattention symptoms (6 weeks PT; parent rated; CPRS inattention subscale; high is poor, 0-18)



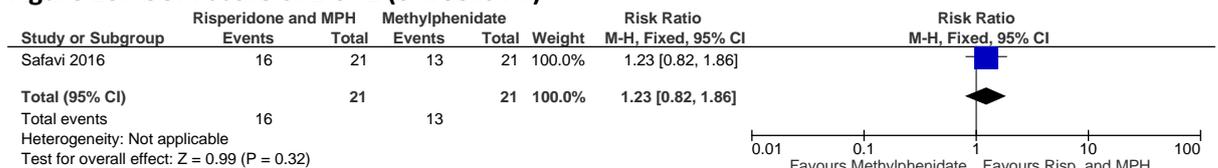
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Figure 12: ADHD hyperactivity symptoms (6 weeks PT; parent rated; CPRS hyperactivity subscale; high is poor, 0-18)



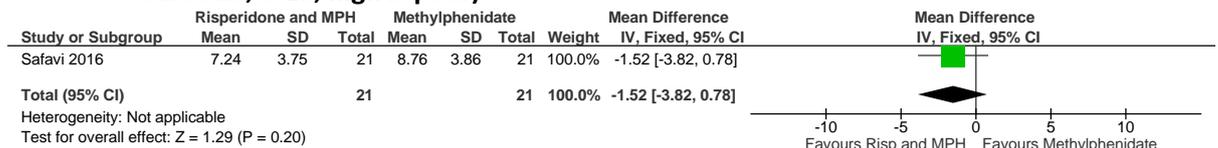
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Figure 13: CGI-I score of 1 or 2 (6 weeks PT)



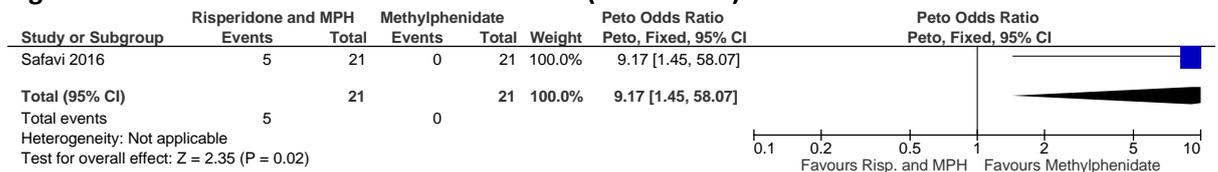
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Figure 14: Behaviour outcomes (6 weeks PT; parent rated; CPRS oppositional defiant disorder subscale; 0-18, high is poor)



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Figure 15: Discontinued due to adverse events (6 weeks PT)

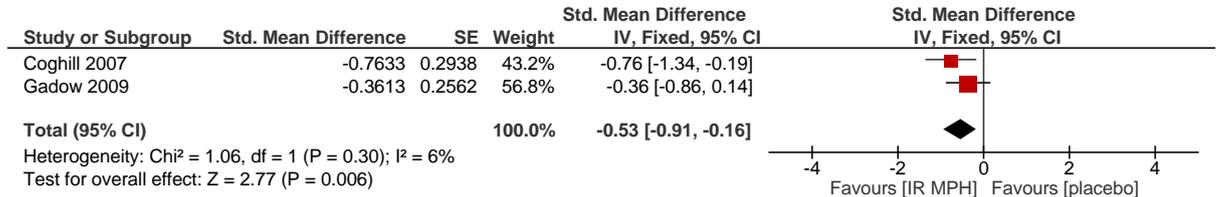


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1 **E.1.2 Children and adolescents (aged 5 to 18)**

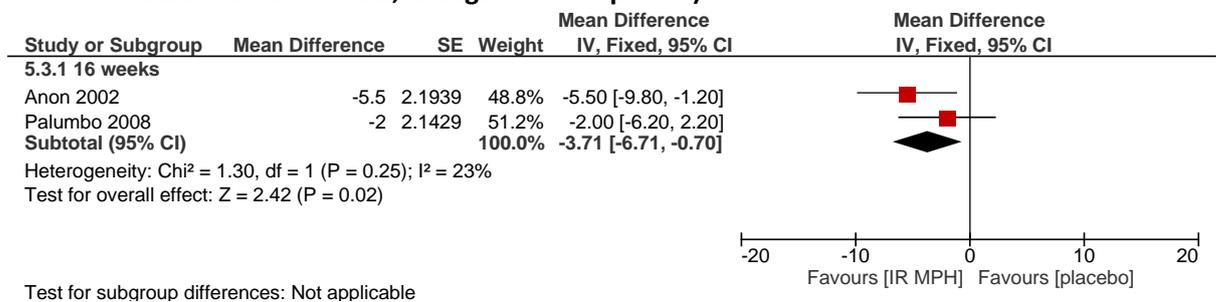
2 **Immediate release methylphenidate versus placebo**

Figure 16: ADHD total symptoms parent rated (4-7 week crossover trials; Abbreviated Parent Rating scale and parent rated ADHD index; lower values are beneficial; final values reported)



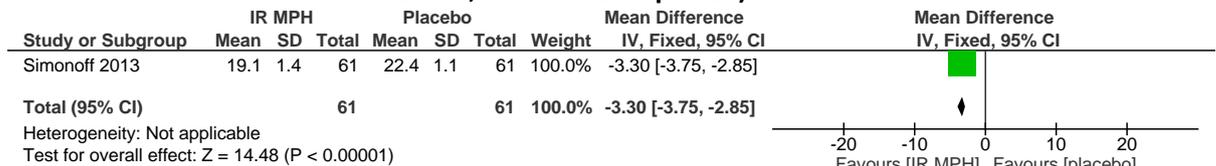
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Figure 17: ADHD total symptoms parent rated (16 weeks PT; ASQ-Parent total score; 0-20; low values are beneficial; change scores reported)



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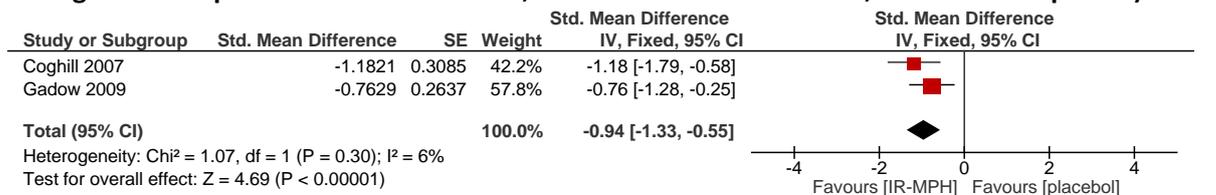
Figure 18: ADHD total symptoms parent rated (16 weeks PT; parent rated ADHD index; 0-30, lower values are beneficial; final values reported)



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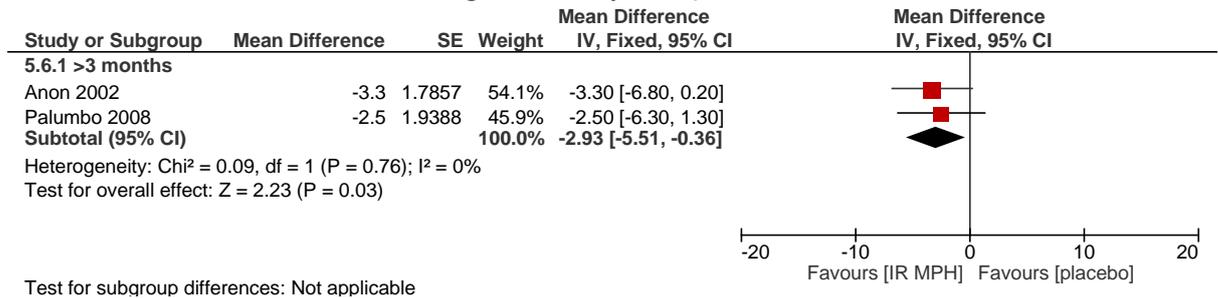
Figure 19: ADHD total symptoms teacher rated (4-7 week crossover trials; Abbreviated Parent Rating scale and parent rated ADHD index; lower values are beneficial; final values reported)



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Figure 20: ADHD total symptoms teacher rated (16 weeks PT, ASQ-teacher total score; 0-20; lower values are beneficial; change scores reported)



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Figure 21: ADHD total symptoms teacher rated (16 weeks PT; parent rated ADHD index; 0-30 lower values are beneficial; final values reported)

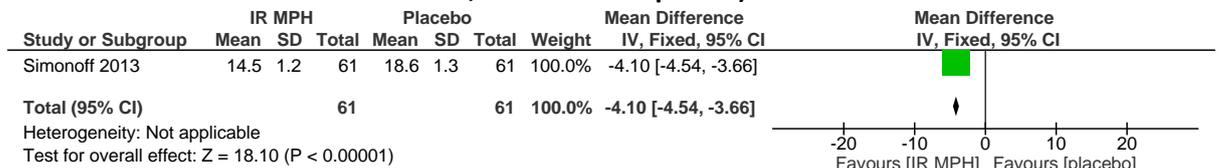


Figure 22: ADHD hyperactivity symptoms parent rated (4-8 weeks; PT; SNAP-IV and Parent Symptom Questionnaire hyperactivity subscales; lower values are beneficial; final values reported)

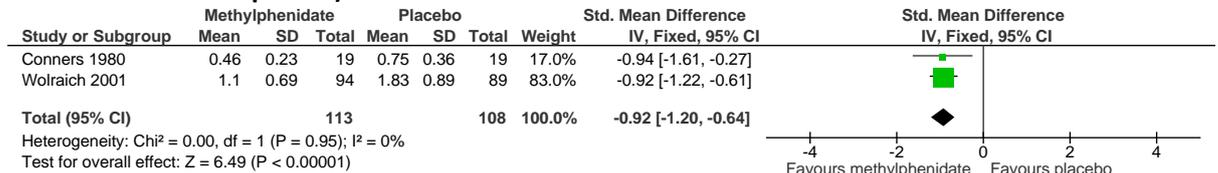


Figure 23: ADHD hyperactivity symptoms parent rated at 16 weeks (Conners Parent ADHD index hyperactive subscale; low scores are beneficial, 0-15)

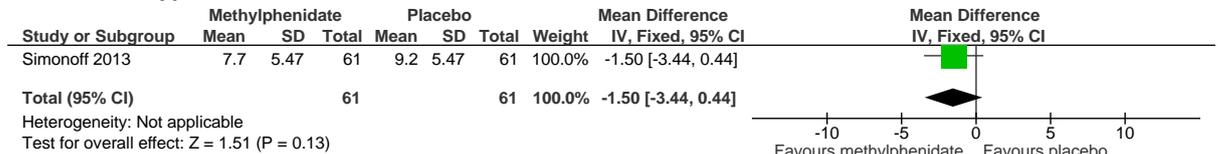


Figure 24: ADHD hyperactivity symptoms teacher rated (4 weeks; PT; SNAP-IV hyperactivity subscales; 0-3; lower values are beneficial)

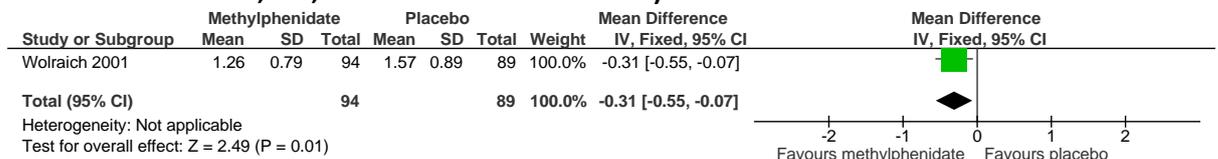
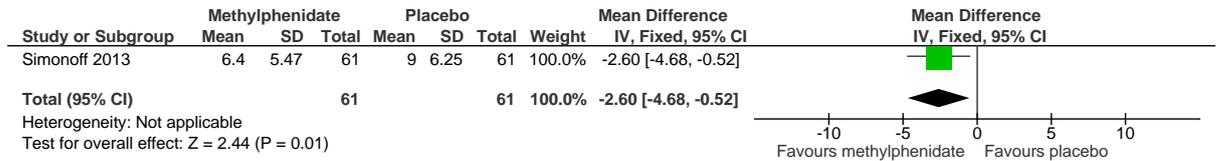


Figure 25: ADHD hyperactivity symptoms teacher rated at 16 weeks (Conners Teacher ADHD index hyperactive subscale; low scores are beneficial, 0-15)



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Figure 26: ADHD inattention symptoms parent rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are beneficial

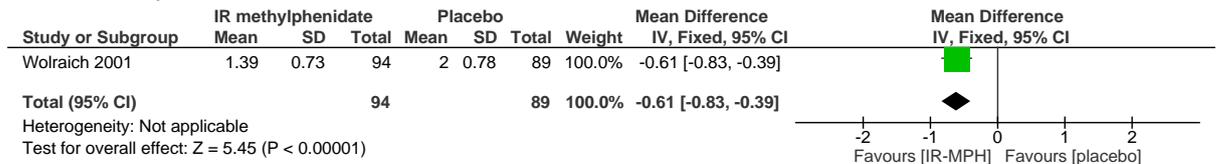


Figure 27: ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are beneficial

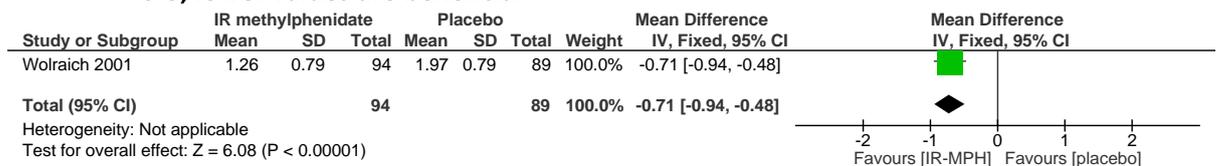
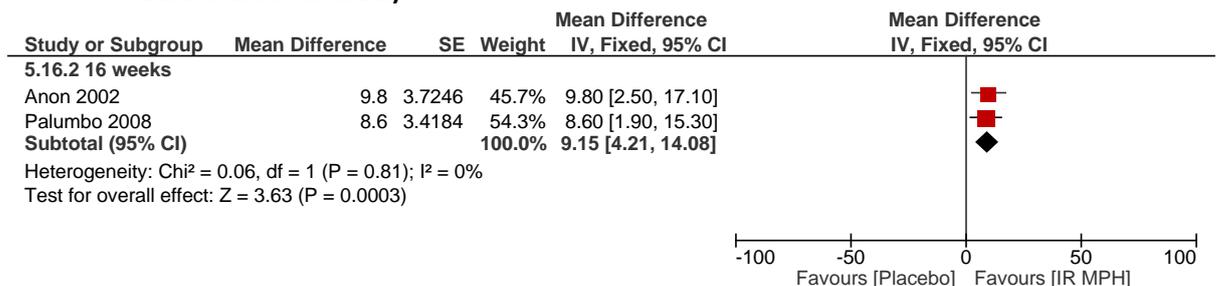


Figure 28: Clinical Global Impressions score of 1 or 2 at 3 to 9 weeks



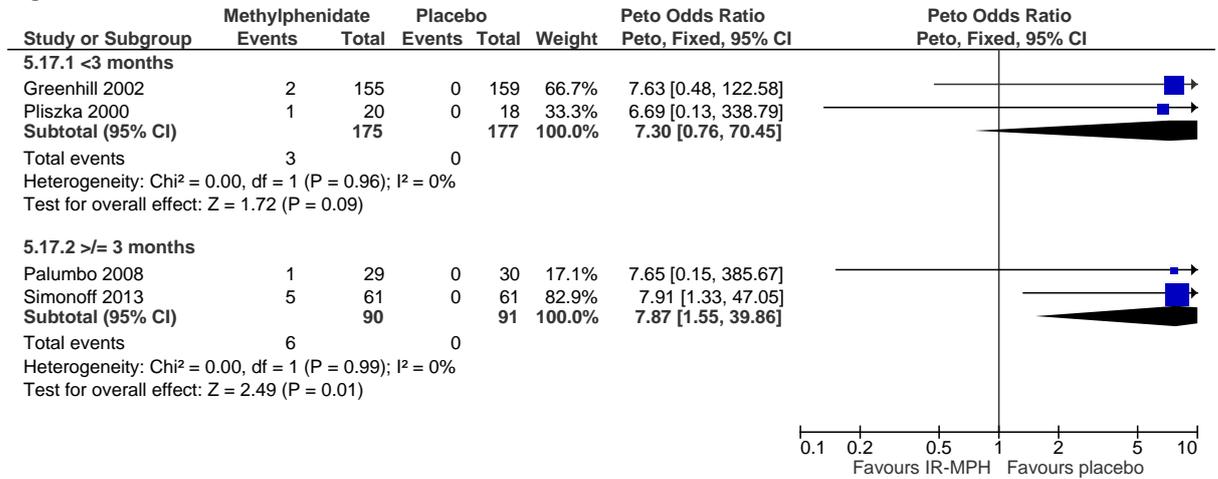
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Figure 29: Behavioural outcomes at 16 weeks (Children's Global Assessment Scale; 0-100; higher values are beneficial)



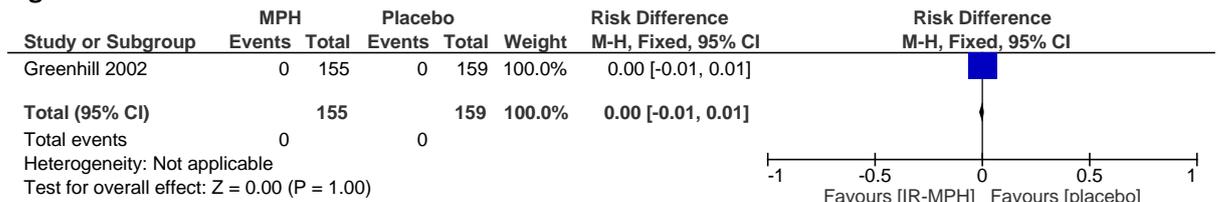
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Figure 30: Discontinuation due to adverse events at 3 to 16 weeks



2

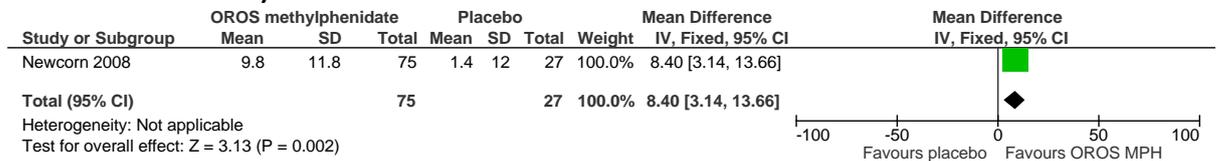
Figure 31: Serious adverse events at 3 weeks



3

4 **OROS methylphenidate versus placebo**

Figure 32: Quality of Life (Child Health Questionnaire at 6 weeks; 0-100, higher values are beneficial)



5

Figure 33: ADHD total symptoms parent rated at 6 weeks (CPRS total scores: 0-54, lower values are beneficial, change scores reported)

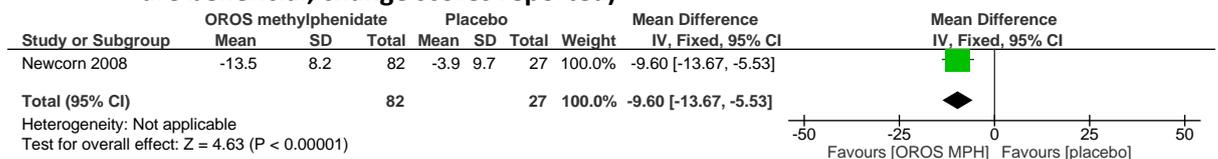
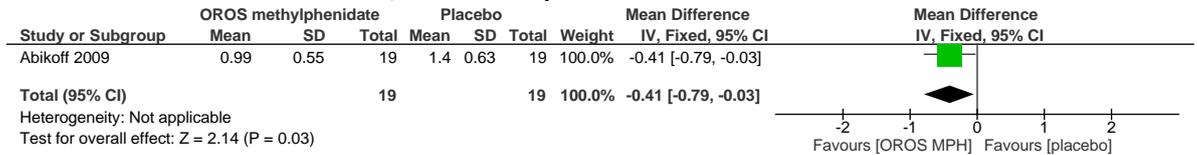
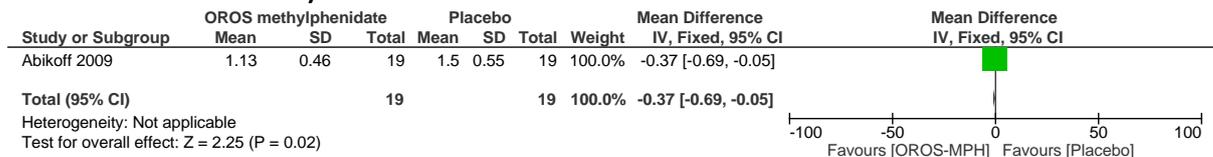


Figure 34: ADHD total symptoms parent rated at 4 weeks (SNAP-IV total scores: 0-3, lower values are beneficial, final values)



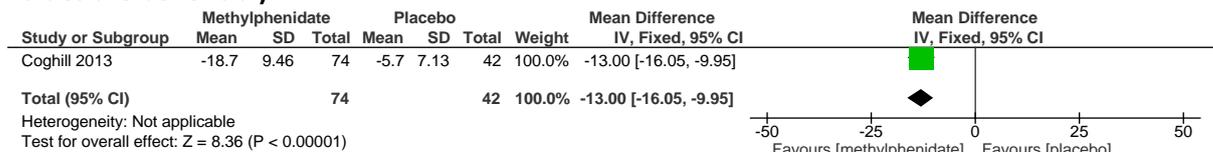
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Figure 35: ADHD total symptoms teacher rated (SNAP-IV total scores at 4 weeks; 0-3; lower values are beneficial)



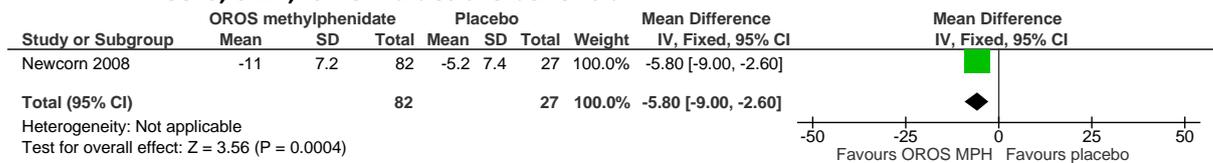
2

Figure 36: ADHD total symptoms investigator rated (7 weeks; ADHD-RS total scores; 0-54; lower values are beneficial)



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Figure 37: ADHD inattention symptoms investigator rated (ADHD-RS Inattentive subscale at 6 weeks; 0-27; lower values are beneficial)



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Figure 38: ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are beneficial)

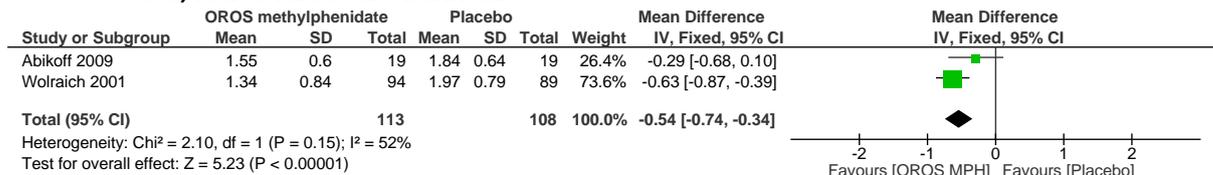
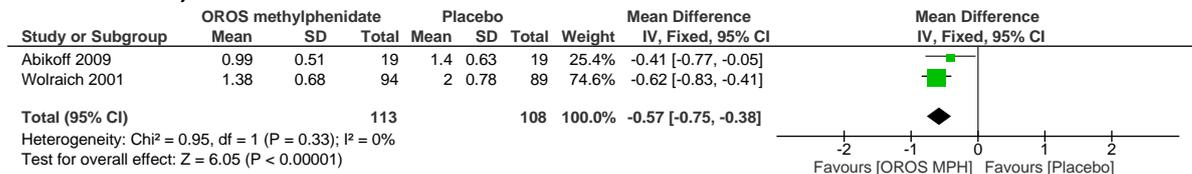
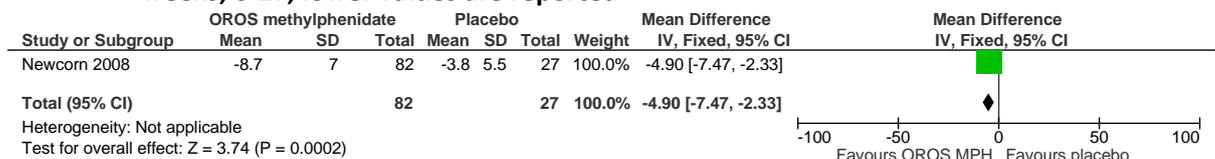


Figure 39: ADHD inattention symptoms parent rated (SNAP-IV inattention subscale) at 4 weeks; 0-3; lower values are beneficial



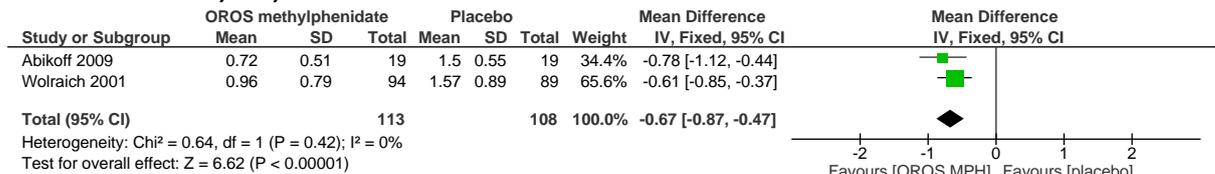
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Figure 40: ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactive subscale) at 6 weeks; 0-27, lower values are reported



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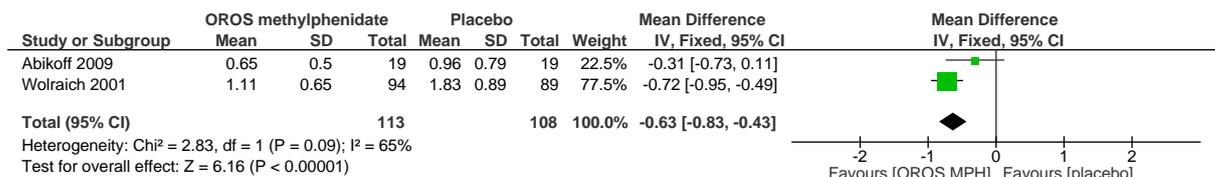
Figure 41: ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale) at 4 weeks; 0-3; lower values are beneficial



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Figure 42: ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale) at 4 weeks; 0-3; lower values are beneficial



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Figure 43: Clinical Global Impressions – Improvement (score of 1 or 2) at 4 to 7 weeks

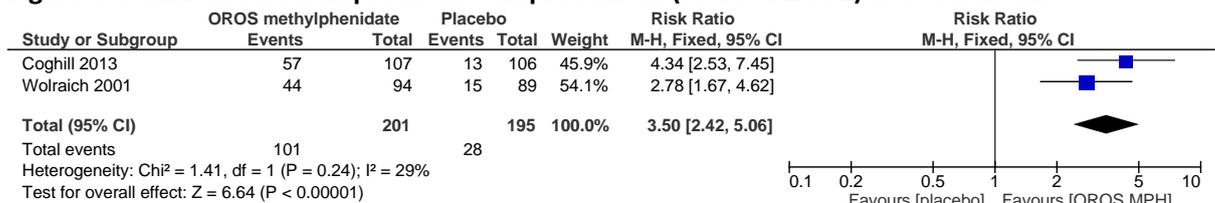


Figure 44: Behavioural outcome at 7 weeks (WFIRS-P; high values are beneficial)

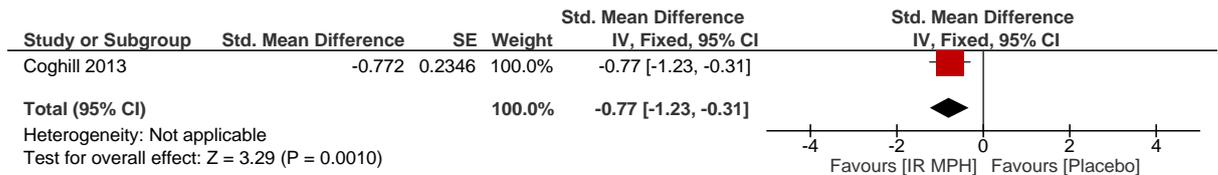


Figure 45: Academic achievement at 7 weeks (CHIP-CE academic achievement subscale); 0-100; high scores are beneficial

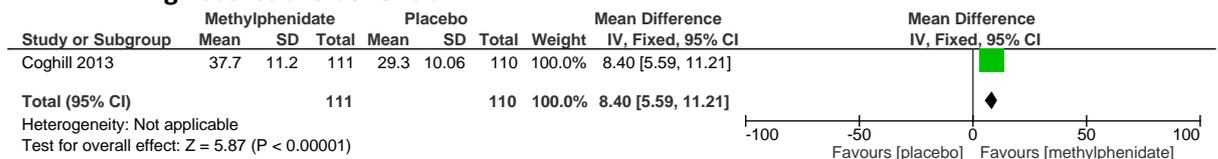
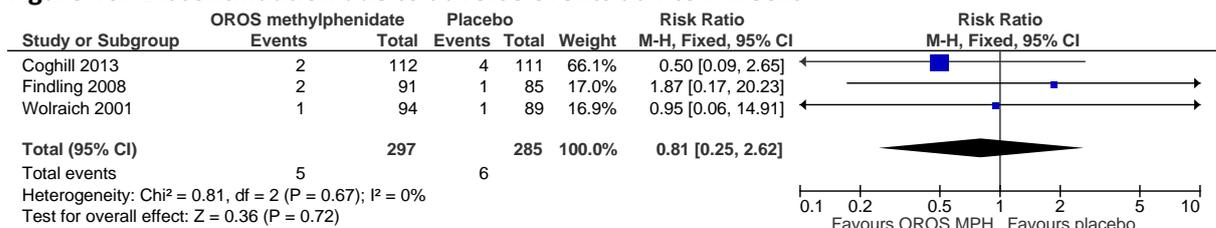


Figure 46: Discontinuation due to adverse events at 4 to 7 weeks



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IR methylphenidate versus OROS methylphenidate

Figure 47: ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale at 4 weeks; 0-3; lower values are beneficial)

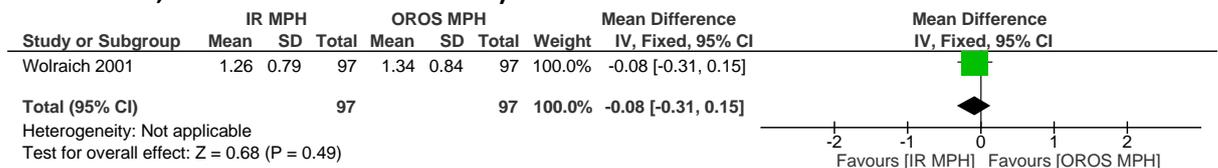
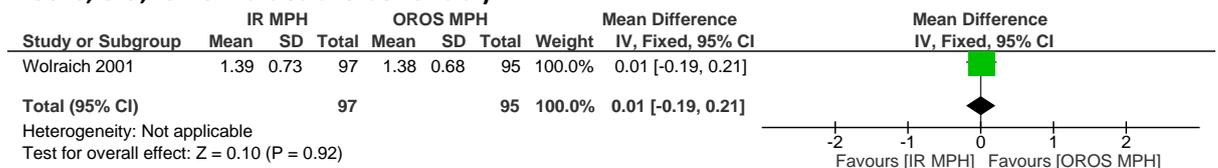


Figure 48: ADHD inattention symptoms parent rated (SNAP-IV inattention subscale at 4 weeks; 0-3; lower values are beneficial)



4

Figure 49: ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale at 4 weeks; 0-3; lower values are beneficial)

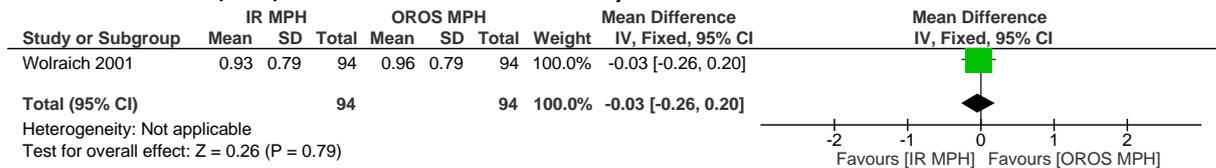
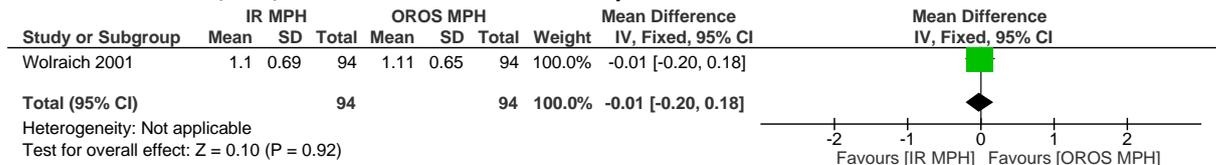
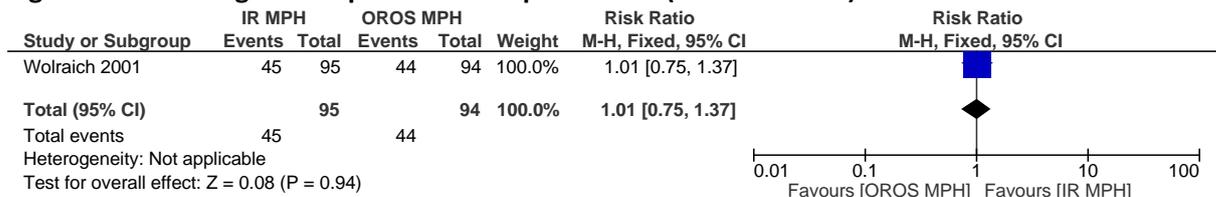


Figure 50: ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale at 4 weeks; 0-3; lower values are beneficial)



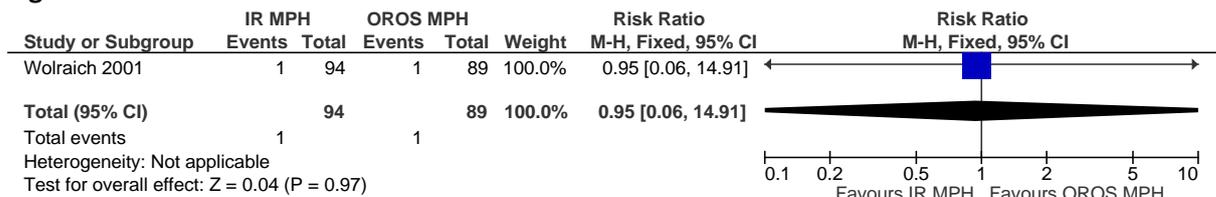
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Figure 51: Clinical global impressions – improvement (score of 1 or 2) at 4 weeks



2

Figure 52: Discontinuation due to adverse events at 4 weeks

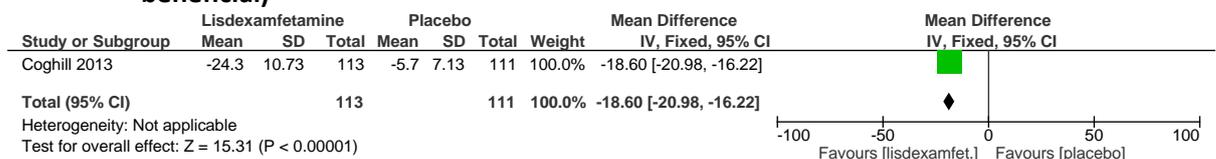


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Lisdexamfetamine versus placebo

Figure 53: ADHD total symptoms investigator rated (ADHD-RS total scores; 0-54, low values are beneficial)

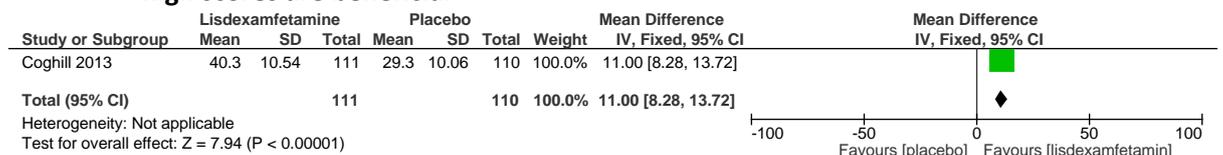


1

Figure 54: CGI-I scores of 1 or 2 at 7 weeks

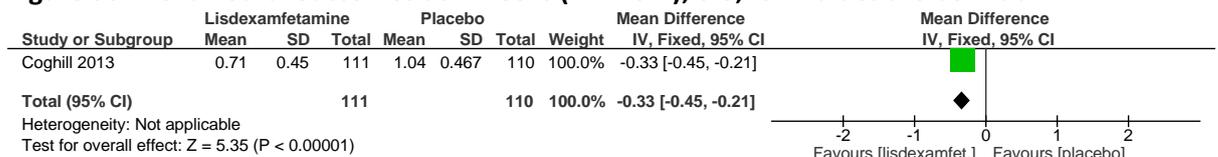


Figure 55: Academic achievement at 7 weeks (CHIP-CE academic achievement subscale); 0-100, high scores are beneficial



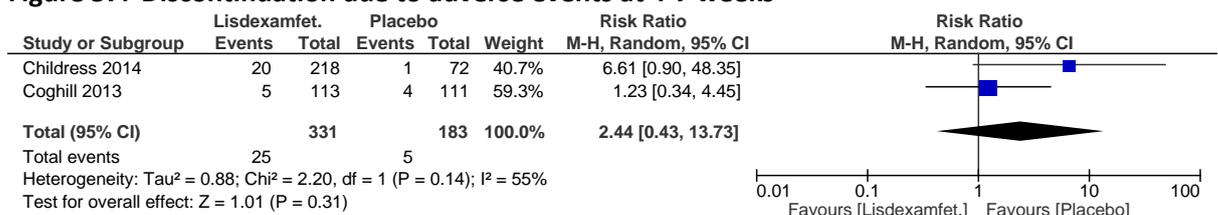
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Figure 56: Behavioural outcomes at 7 weeks (WFIRS-P); 0-3; low values are beneficial



3

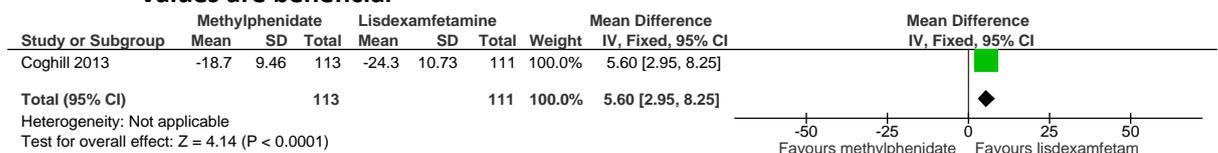
Figure 57: Discontinuation due to adverse events at 4-7 weeks



4

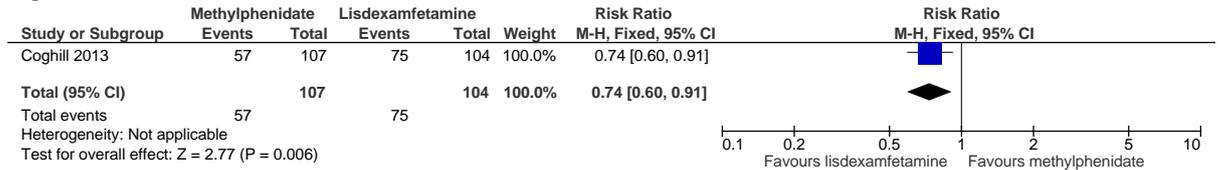
Methylphenidate versus lisdexamfetamine

Figure 58: ADHD total symptoms investigator rated at 7 weeks (ADHD-RS total scores); 0-72; low values are beneficial



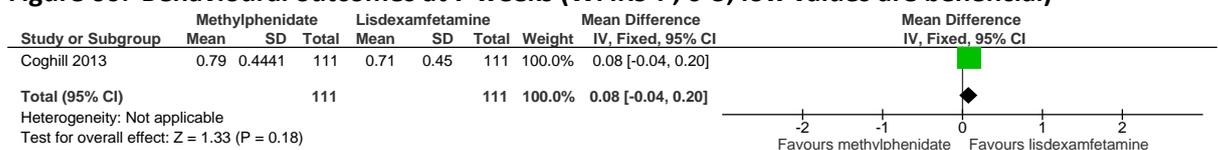
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Figure 59: CGI-I scores of 1 or 2 at 7 weeks



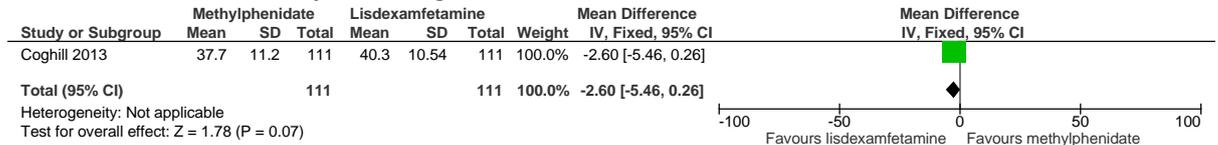
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Figure 60: Behavioural outcomes at 7 weeks (WFIRS-P; 0-3; low values are beneficial)



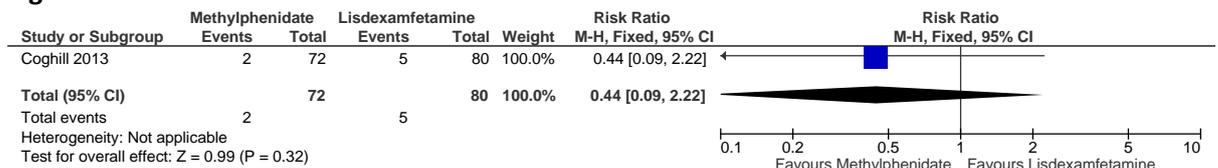
3

Figure 61: Academic achievement at 7 weeks (CHIP-CE academic achievement subscale); 0-100, final values reported; high scores are beneficial



4

Figure 62: Discontinuation due to adverse events at 7 weeks



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Atomoxetine versus placebo

Figure 63: Quality of Life at 8 to 10 weeks (CHQ and CHIP-CE; change scores reported; high values are beneficial)

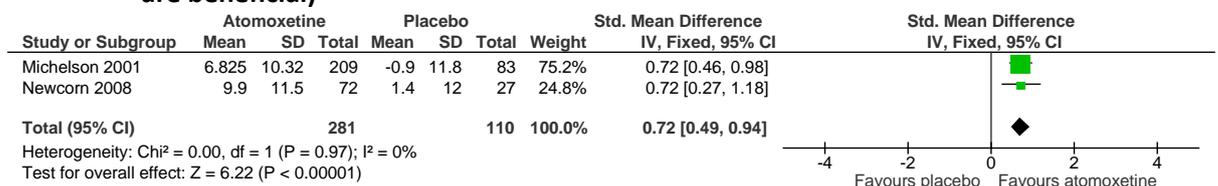
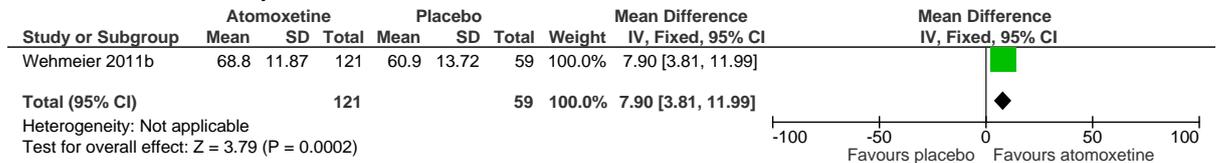
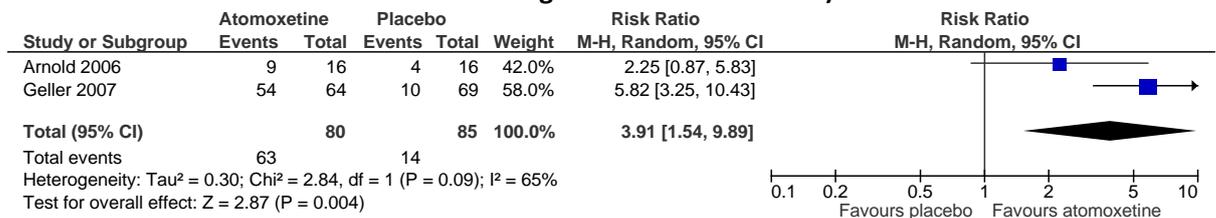


Figure 64: Quality of Life at 8 to 10 weeks (KINDL-R; 0-100; final values reported; high values are beneficial)



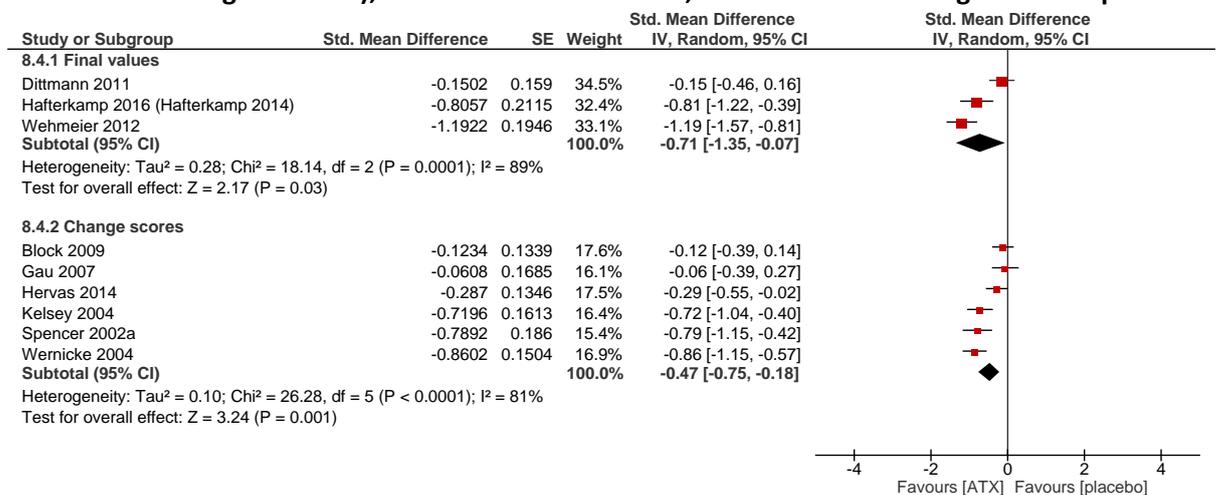
1

Figure 65: Treatment response at 6 to 12 weeks (defined as 25% reduction in ABC-H and CGI-I of 1 or 2 or a 25% reduction on ADHD-RS investigator rated total scores)



2

Figure 66: ADHD total symptoms at 6 to 13 weeks (ADHD-RS and SNAP-IV total scores; investigator rated); low scores are beneficial, final values and change scores reported



3

Figure 67: ADHD total symptoms teacher rated at 6 to 9 weeks (multiple scales including ADHD-RS and SNAP-IV total scores; low scores are beneficial)

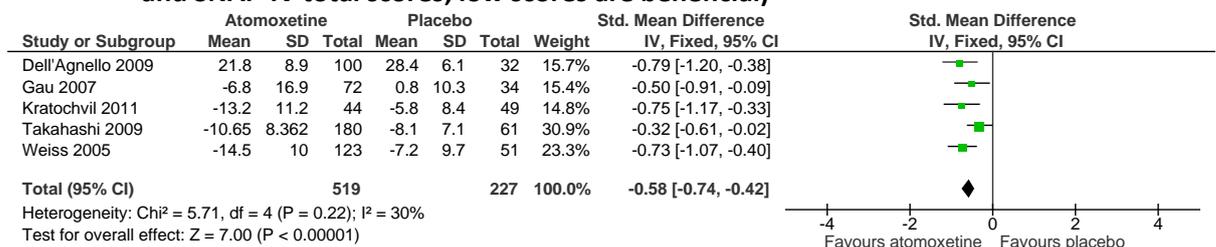
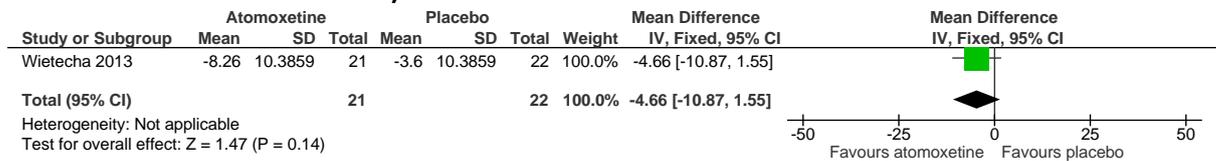


Figure 68: ADHD total symptoms teacher rated at 16 weeks (ADHD-RS total scores; 0-54, low scores are beneficial)



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Figure 69: ADHD total symptoms parent rated at 4 to 12 weeks (multiple scales including ADHD-RS and CPRS total scores; low scores are beneficial; change scores reported)

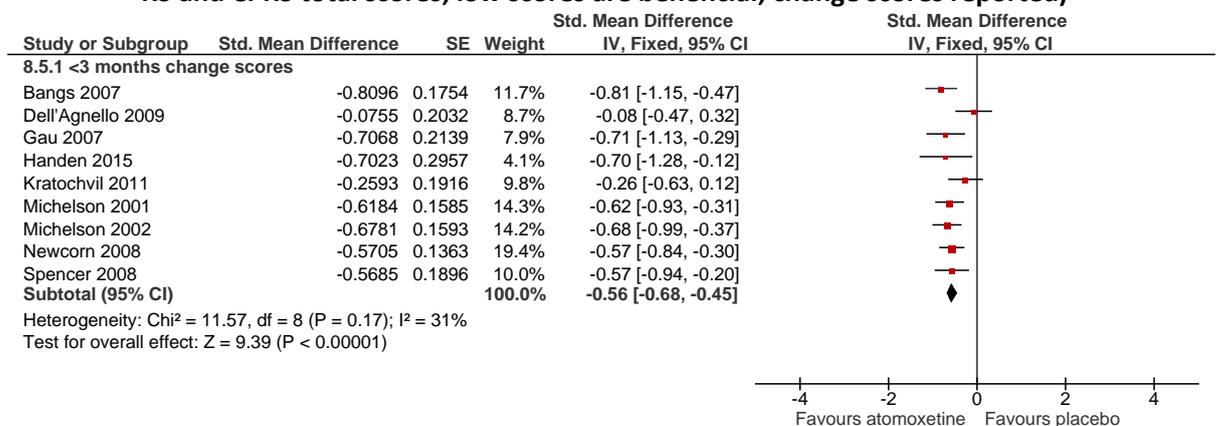
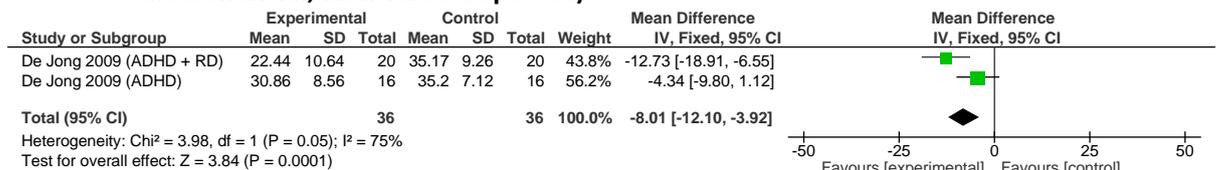


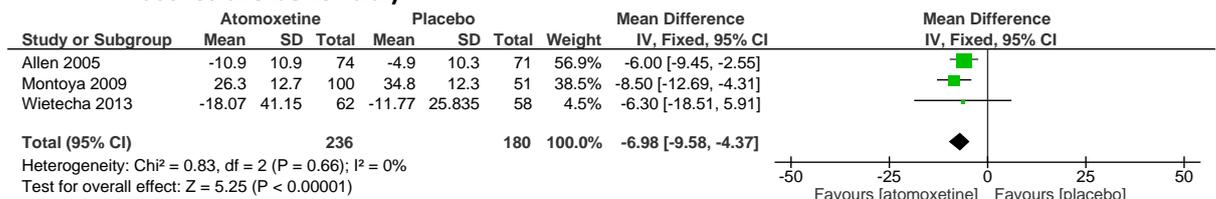
Figure 70: ADHD total symptoms parent rated at 4 weeks (ADHD-RS total scores; 0-54; low scores are beneficial; final values reported)



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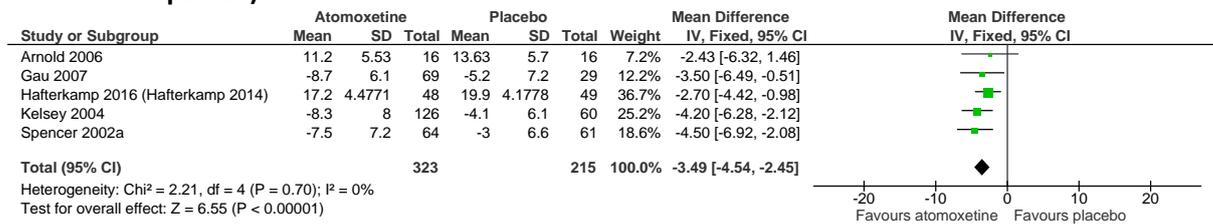
Figure 71: ADHD total symptoms parent rated at 12-18 weeks (ADHD-RS total scores; 0-54; low scores are beneficial)



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Figure 72: ADHD inattention symptoms at 6 to 9 weeks (ADHD-RS inattentive subscale Investigator rated; 0-27; low scores are beneficial; final values and change scores reported)



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Figure 73: ADHD inattention symptoms at 6 to 16 weeks (ADHD-RS inattentive subscale teacher rated; 0-27; low scores are beneficial)

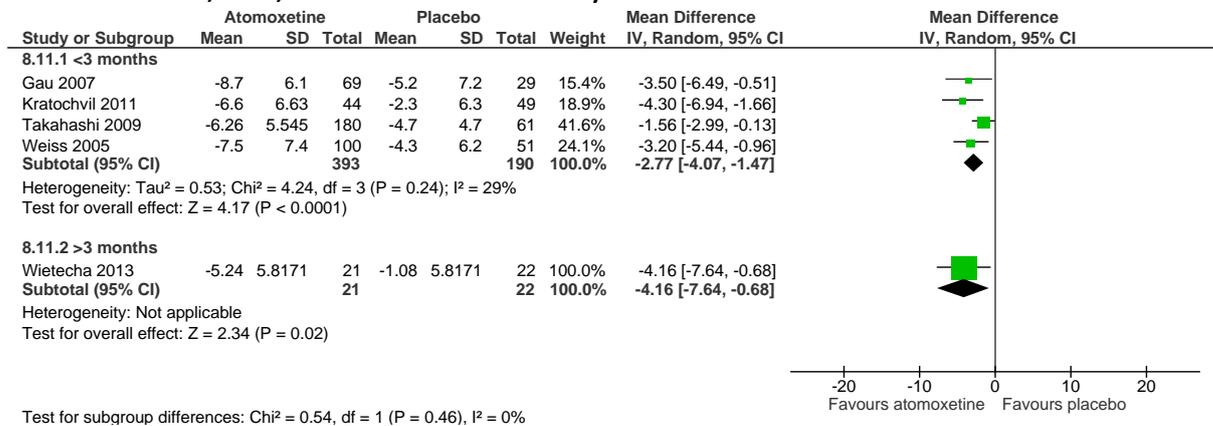


Figure 74: ADHD inattention symptoms at 4 to 12 weeks (ADHD-RS and SNAP-IV inattentive subscale; parent rated); low scores are beneficial; change scores reported

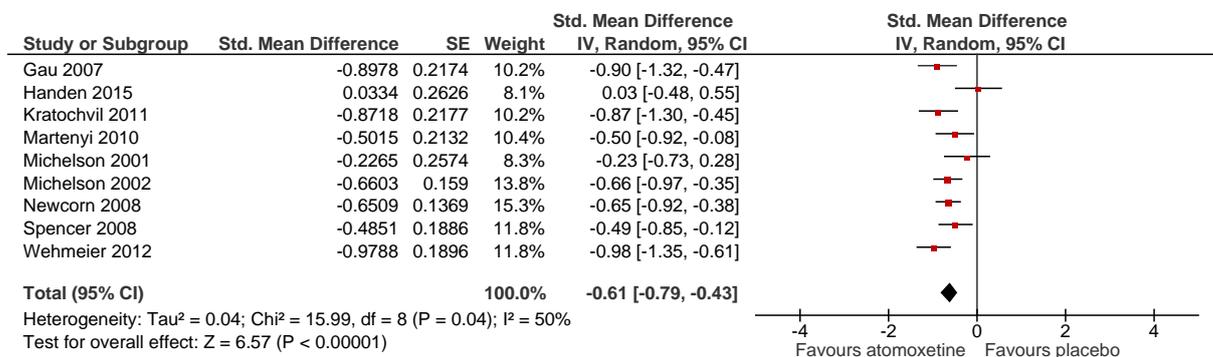
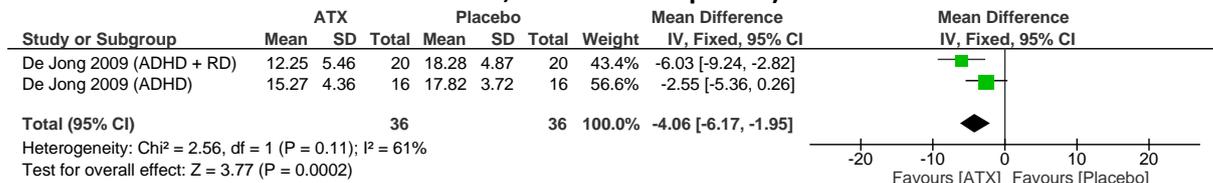
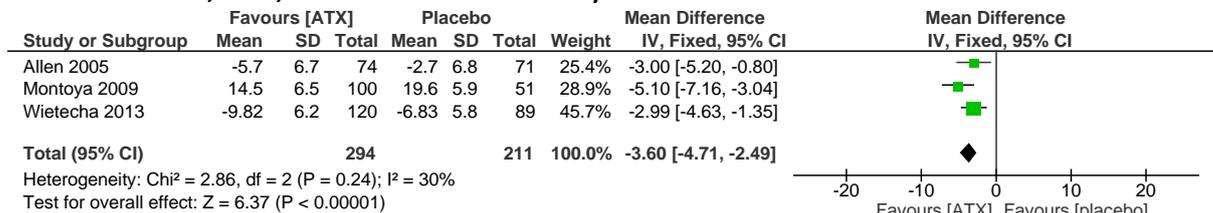


Figure 75: ADHD inattention symptoms at 4 weeks (ADHD-RS inattentive subscale; parent rated; 0-27 low scores are beneficial; final values reported)



1

Figure 76: ADHD inattention symptoms at 12 to 18 weeks (ADHD-RS inattentive subscale; parent rated; 0-27; low scores are beneficial)



2

Figure 77: ADHD hyperactivity symptoms at 6 to 9 weeks (ADHD-RS hyperactivity subscale, investigator rated); 0-27; low values are beneficial, change scores and final values reported

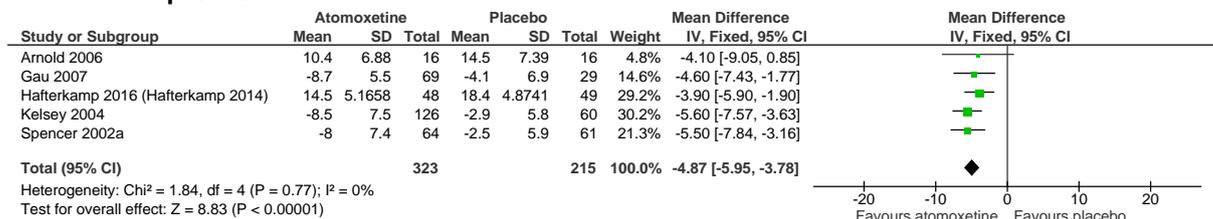
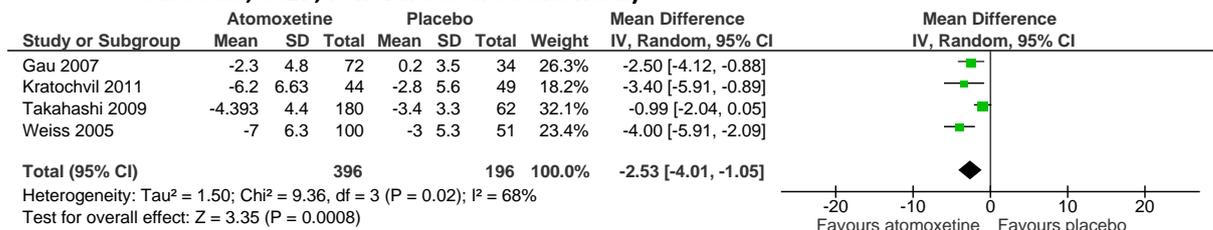
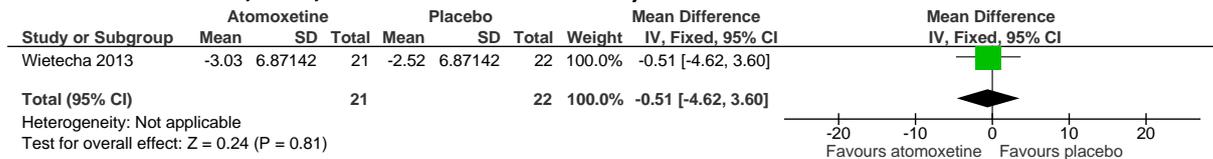


Figure 78: ADHD hyperactivity symptoms teacher rated at 4 to 12 weeks (ADHD-RS hyperactivity subscale; 0-27; low values are beneficial)



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Figure 79: ADHD hyperactivity symptoms teacher rated at 18 weeks (ADHD-RS hyperactivity subscale; 0-27; low values are beneficial)



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Figure 80: ADHD hyperactivity symptoms parent rated at 4 to 12 weeks (multiple scales including ADHD-RS and CPRS hyperactivity subscales; low values are beneficial; change scores reported)

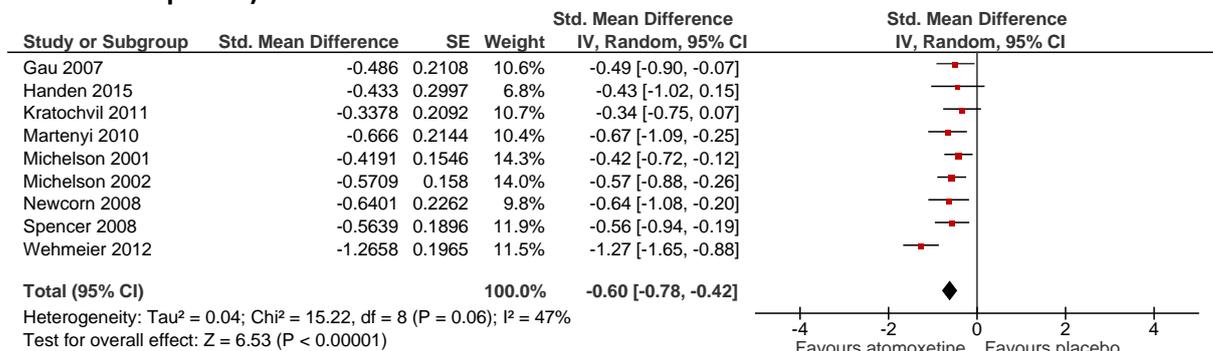


Figure 81: ADHD hyperactivity symptoms at 4 weeks (ADHD-RS hyperactivity subscale, parent rated; 0-27; low values are beneficial; final values reported)

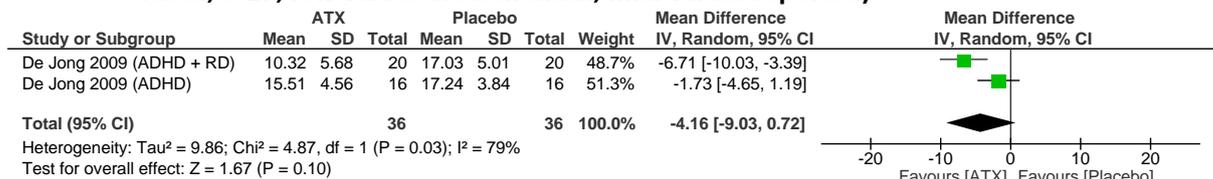


Figure 82: ADHD hyperactivity symptoms at 12 to 18 weeks (ADHD-RS hyperactivity subscales, parent rated; 0-27; low values are beneficial)

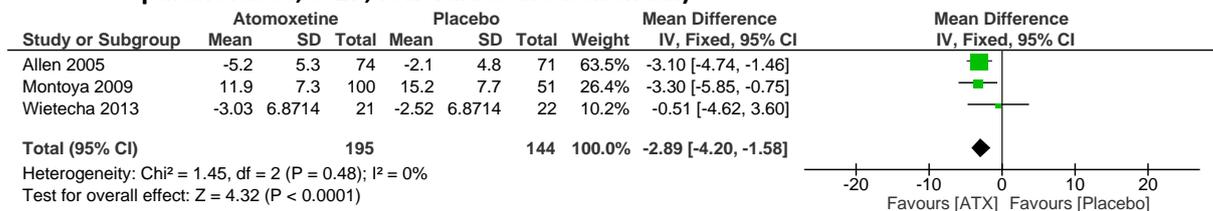
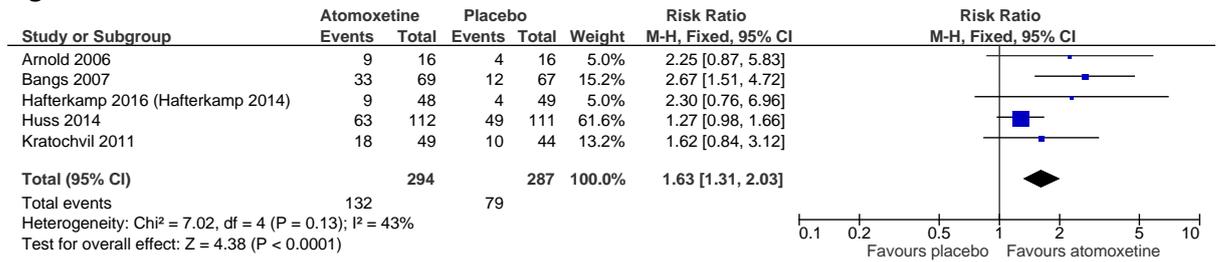
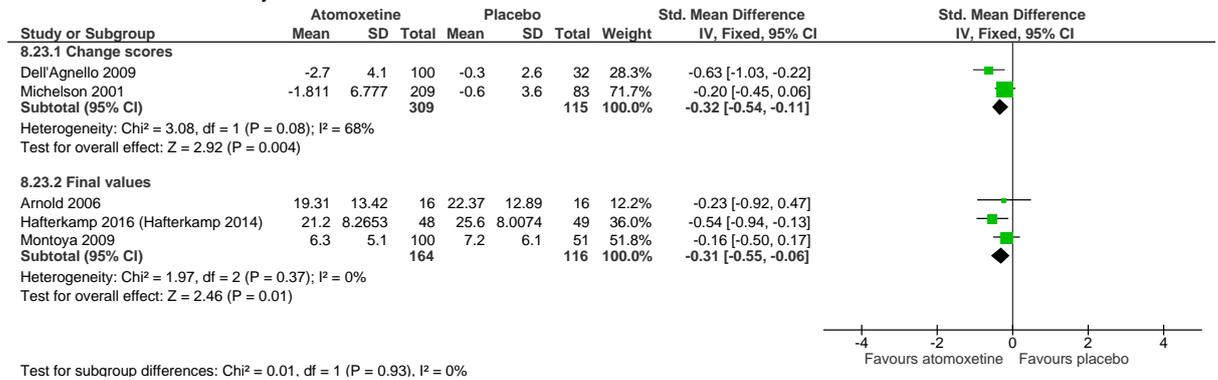


Figure 83: CGI-I score of 1 or 2 at 4 to 13 weeks



1

Figure 84: Behavioural measures at 6 to 12 weeks (multiple scales including ABC and childrens' social behaviour questionnaire; final values and change scores, low scores are beneficial)



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Figure 85: Academic achievement at 12 weeks (CHIP-PRF Achievement subscale; high scores are beneficial, range 0-30)

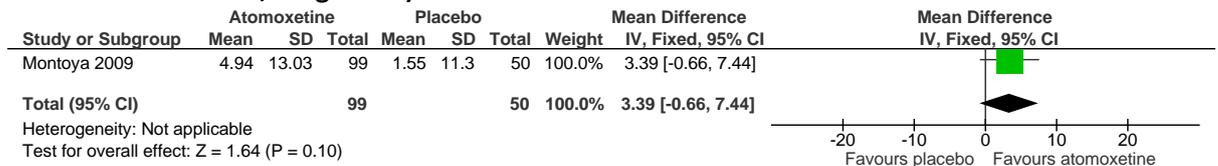
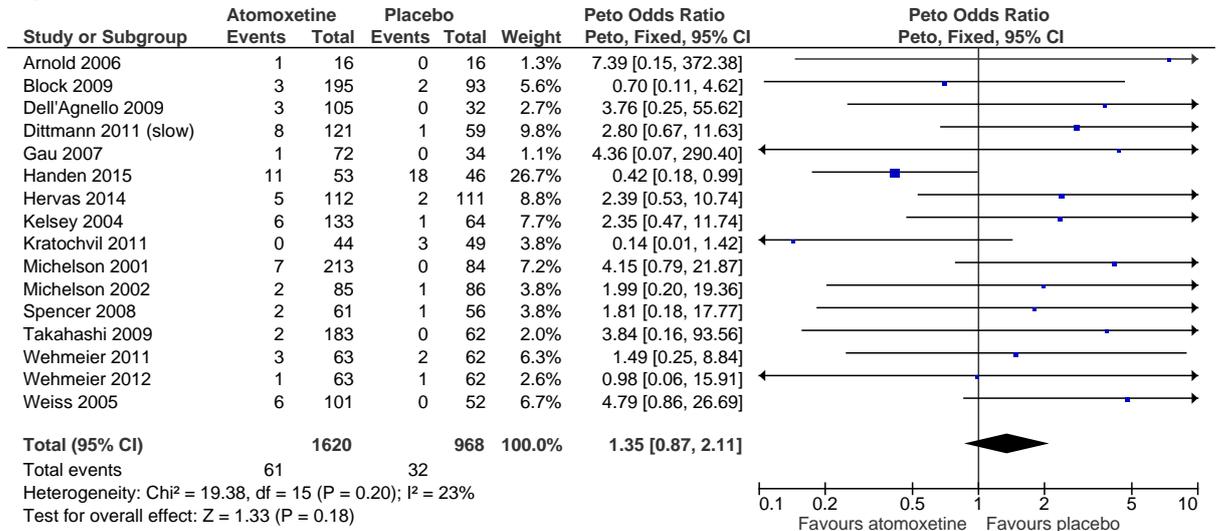
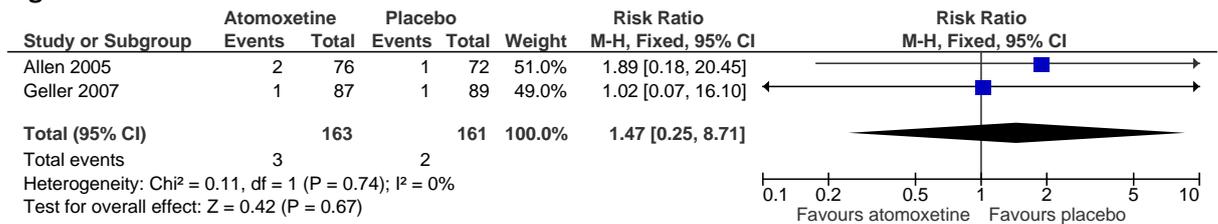


Figure 86: Discontinuation due to adverse events at 3 to 10 weeks



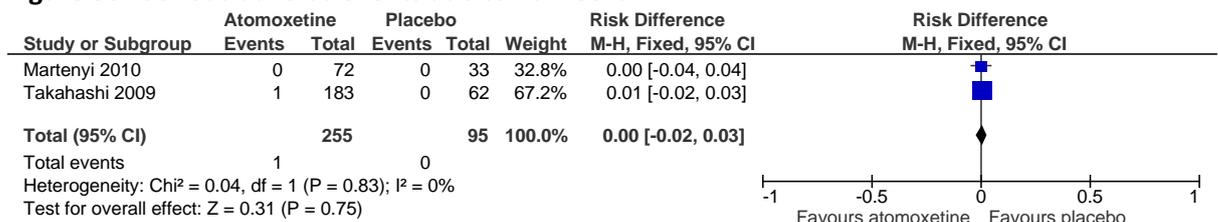
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Figure 87: Discontinuation due to adverse events at 12-18 weeks



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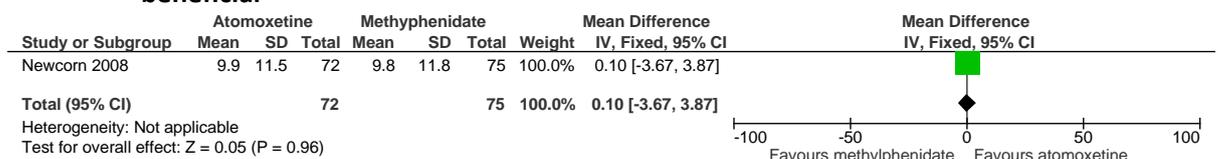
Figure 88: Serious adverse events at 6 to 10 weeks



3

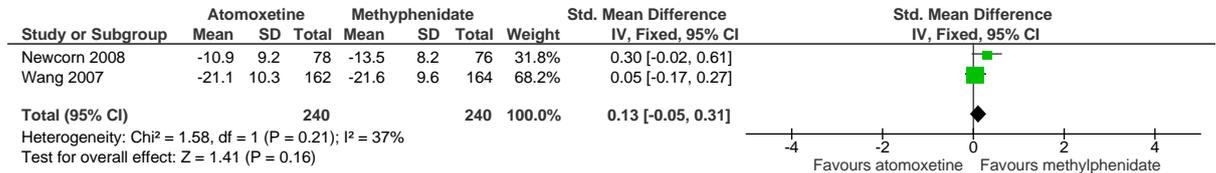
Atomoxetine versus methylphenidate

Figure 89: Quality of life (Child Health Questionnaire) at 6 weeks; 0-100, higher values are beneficial



1

Figure 90: ADHD total symptoms parent rated (CPRS and ADHD-RS total scores) at 6-8 weeks; lower values are beneficial



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Figure 91: ADHD inattention symptoms parent rated (CPRS and ADHD-RS inattentive subscale; at 6-8 weeks; lower values are beneficial)

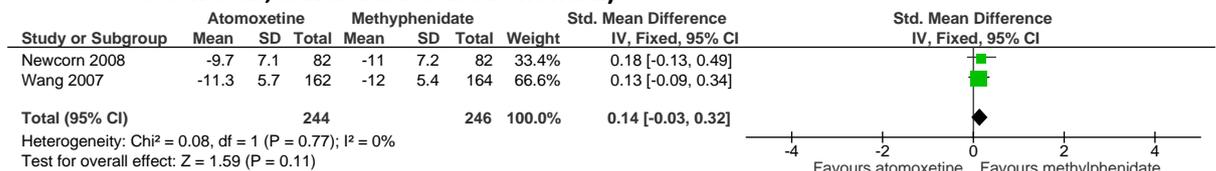


Figure 92: ADHD hyperactivity symptoms parent rated (CPRS and ADHD-RS hyperactive subscale) at 6-8 weeks; lower values are beneficial

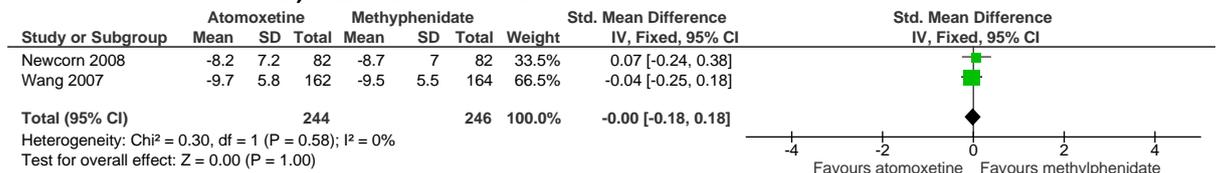
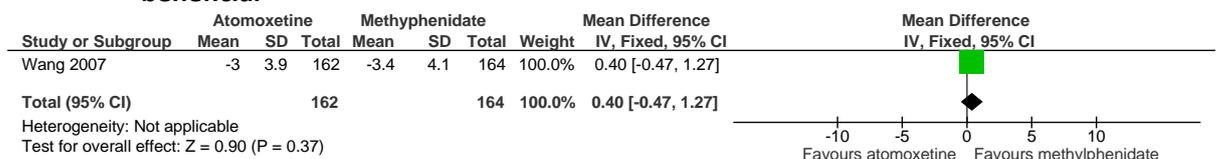
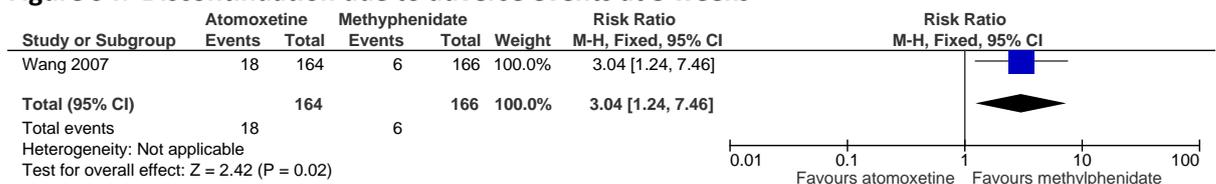


Figure 93: Behavioural outcomes (CPRS Oppositional subscale) at 8 weeks; 0-18; lower values are beneficial



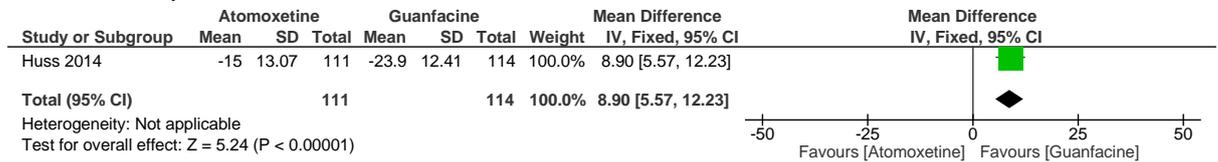
3

Figure 94: Discontinuation due to adverse events at 8 weeks



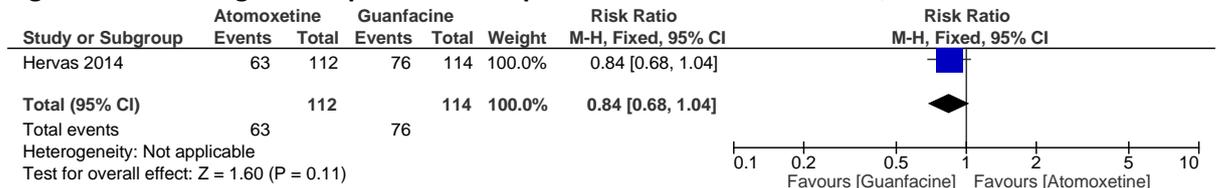
1 **Atomoxetine versus guanfacine ER**

Figure 95: ADHD total symptoms investigator rated (ADHD-RS total scores) at 10 to 13 weeks; 0-54; lower values are beneficial



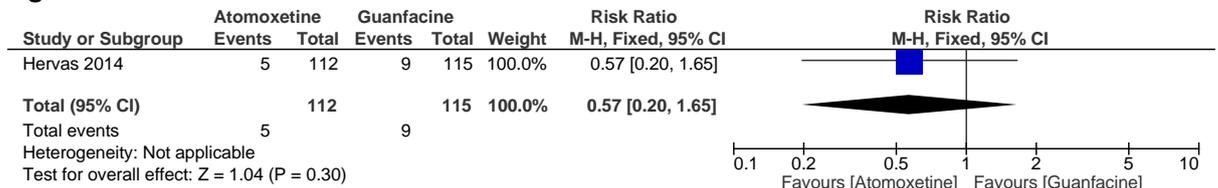
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Figure 96: Clinical global impressions – improvement at 10 to 13 weeks; scores of 1 or 2



3

Figure 97: Discontinuation due to adverse events at 10 to 13 weeks



4

5 **Guanfacine versus placebo**

Figure 98: ADHD total symptoms investigator rated (ADHD-RS total scores) at 8 weeks; 0-54; low values are beneficial

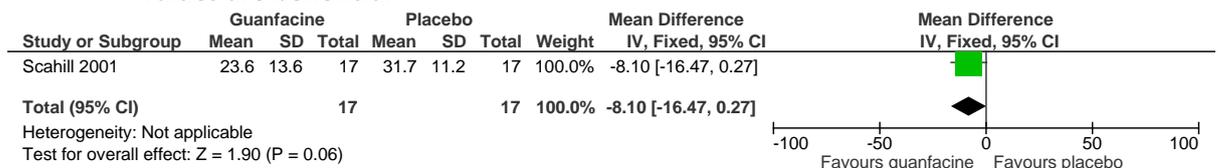


Figure 99: ADHD inattention symptoms investigator rated (ADHD-RS inattentive subscale) at 8 weeks; 0-27, low values are beneficial

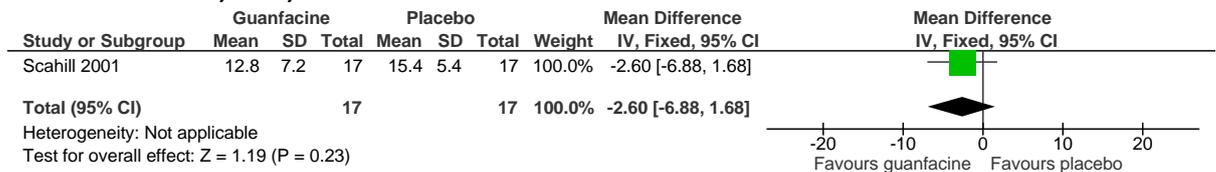
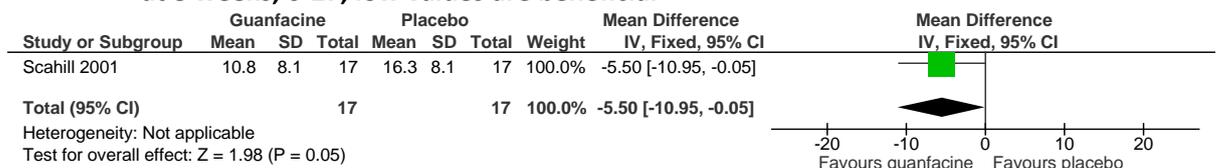
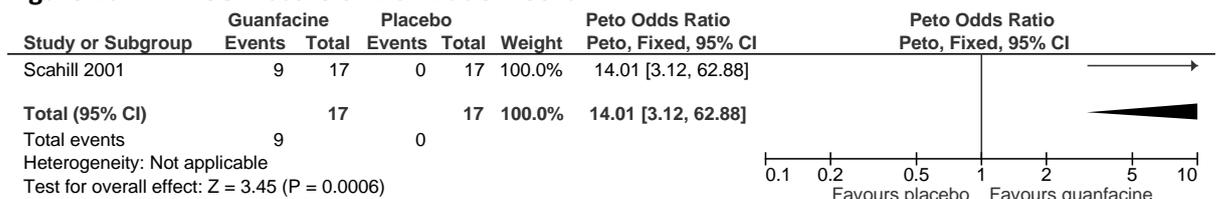


Figure 100: ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactive subscale) at 8 weeks; 0-27, low values are beneficial



1

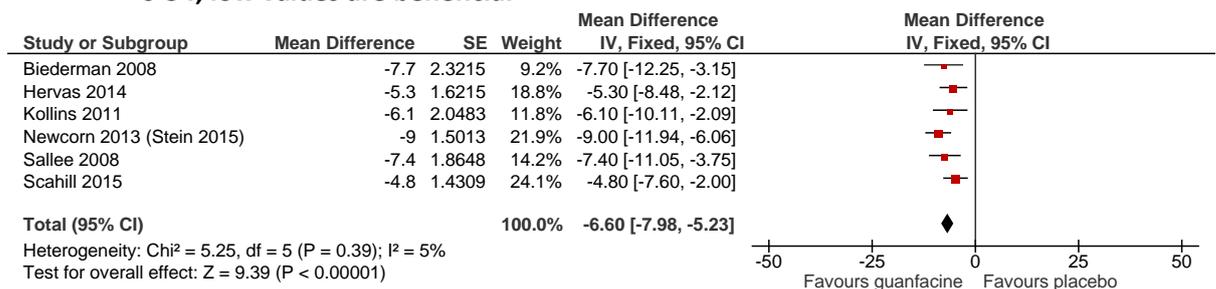
Figure 101: CGI-I score of 1 or 2 at 8 weeks



2

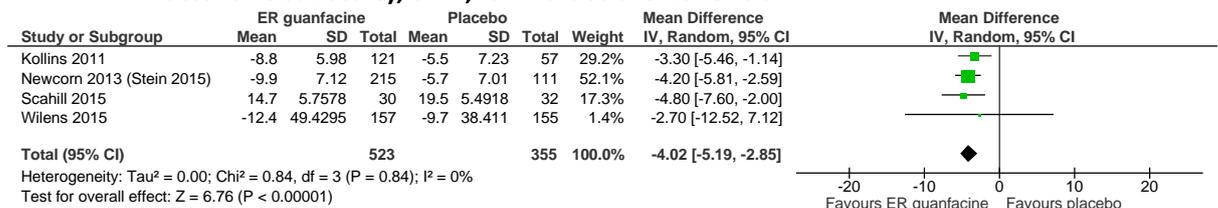
Extended release guanfacine versus placebo

Figure 102: ADHD total symptoms investigator rated at 5 to 13 weeks (ADHD-RS total scores); 0-54; low values are beneficial



3

Figure 103: ADHD inattention symptoms investigator rated at 6 to 8 weeks (ADHD-RS inattentive subscale); 0-27; low values are beneficial



1

Figure 104: ADHD hyperactivity symptoms investigator rated at 6 to 8 weeks (ADHD-RS hyperactive/impulsive subscale; 0-27 ; low values are beneficial; change scores reported)

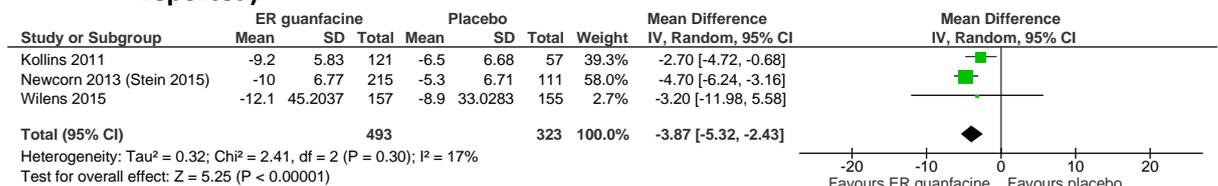
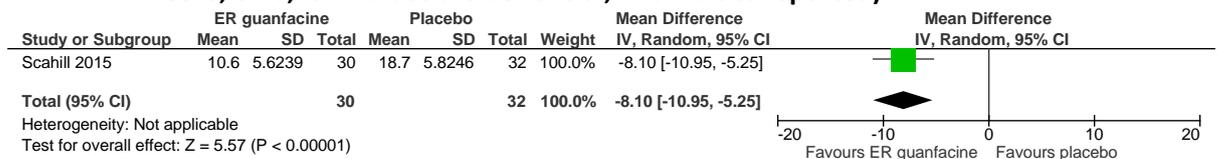
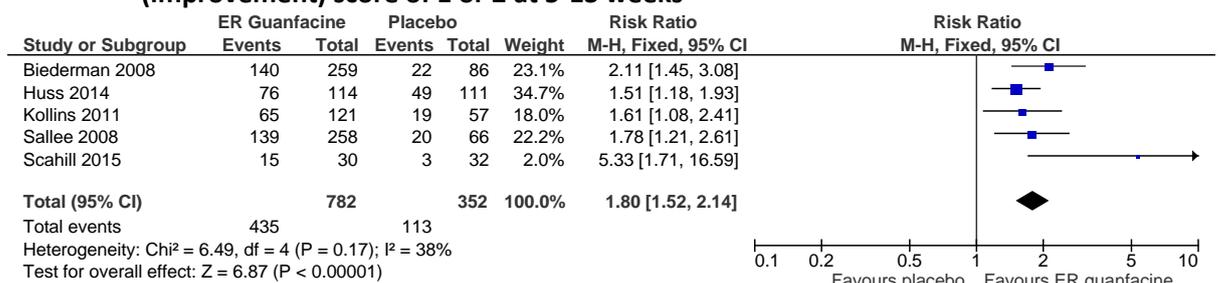


Figure 105: ADHD hyperactivity symptoms investigator rated (ABC hyperactive subscale at 8 weeks; 0-20, low values are beneficial; final values reported)



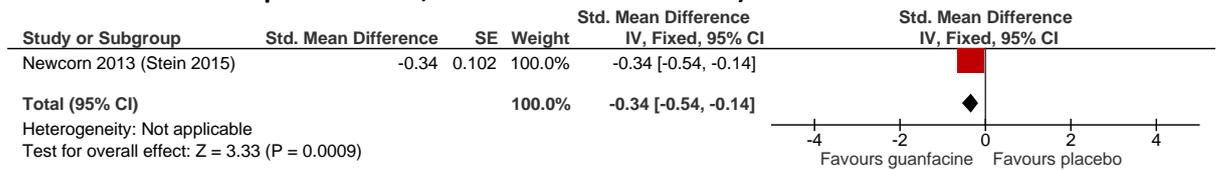
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Figure 106: Clinical Global Impressions (improvement) score of 1 or 2 at 5-13 weeks



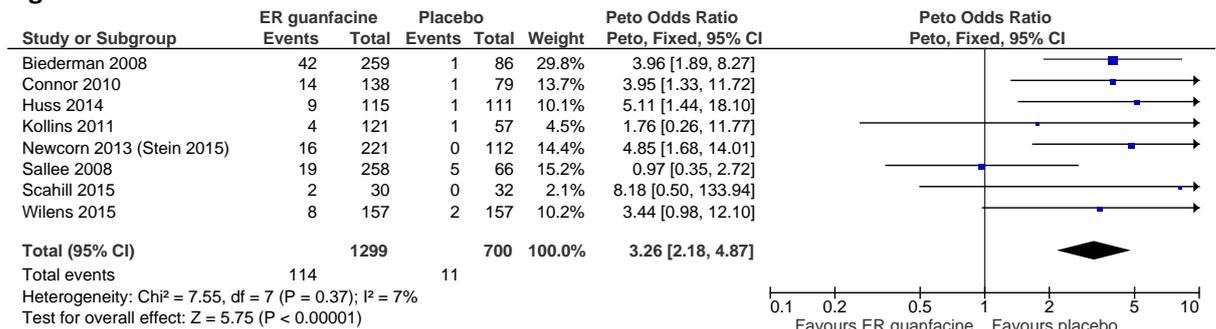
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Figure 107: Academic achievement at 8 weeks (Weiss functional impairment rating scale academic performance, low scores are beneficial)



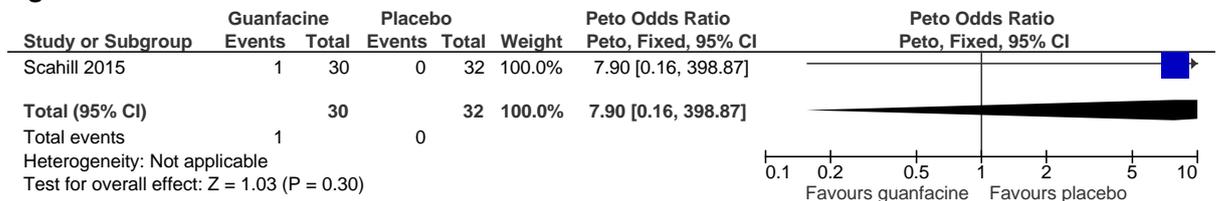
1

Figure 108: Discontinuation due to adverse events at 5 to 13 weeks



2

Figure 109: Serious adverse events at 8 weeks



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Clonidine versus placebo

Figure 110: ADHD total symptoms parent rated at 16 weeks (Conners ASQ-P total score; 0-20 low values are beneficial)

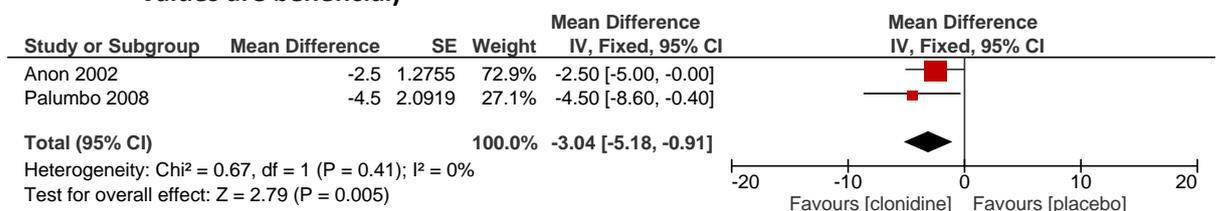


Figure 111: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total score; 0-20, low values are beneficial)

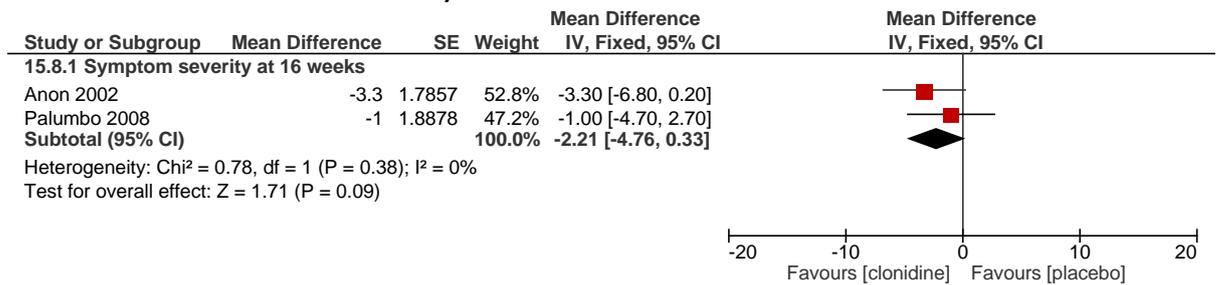


Figure 112: ADHD total symptoms investigator rated at 16 weeks (ADHD-RS total scores); 0-27 low values are beneficial

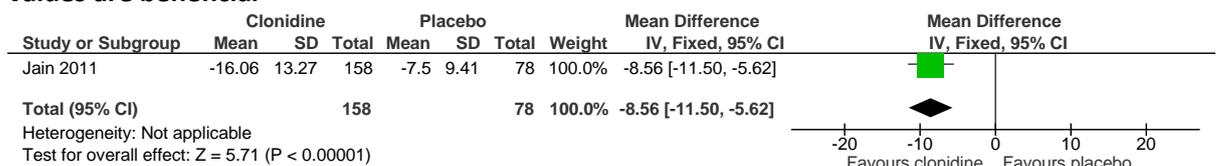
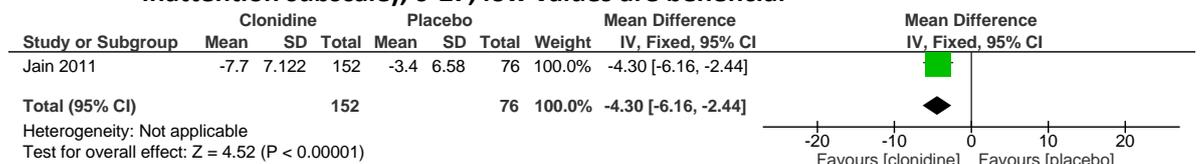


Figure 113: ADHD inattention symptoms investigator rated at 16 weeks (ADHD-RS inattention subscale); 0-27, low values are beneficial



1

Figure 114: ADHD hyperactivity symptoms investigator rated at 16 weeks (ADHD RS hyperactivity subscale); 0-27, lower values are beneficial

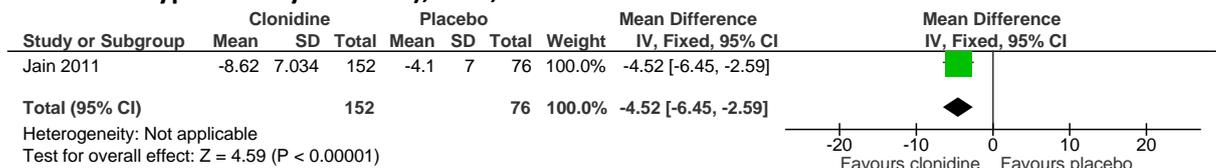
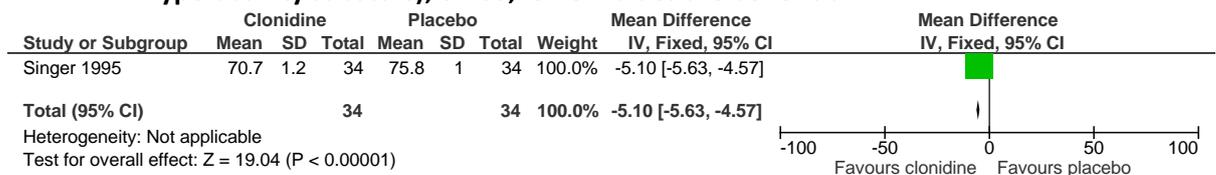
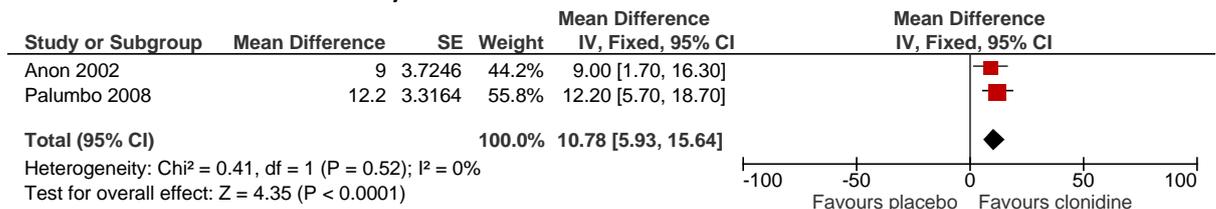


Figure 115: ADHD hyperactivity symptoms parent rated at 6 weeks (Mother/Teacher CBCL Hyperactivity subscale); 0-100, lower values are beneficial



2

Figure 116: Behaviour outcome at 16 weeks (Children's Global Assessment Scale; 0-100, higher values are beneficial)



1

Figure 117: Discontinuation due to adverse events at 16 weeks

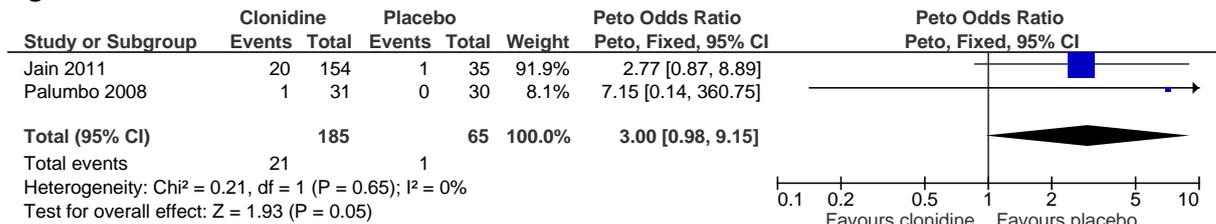
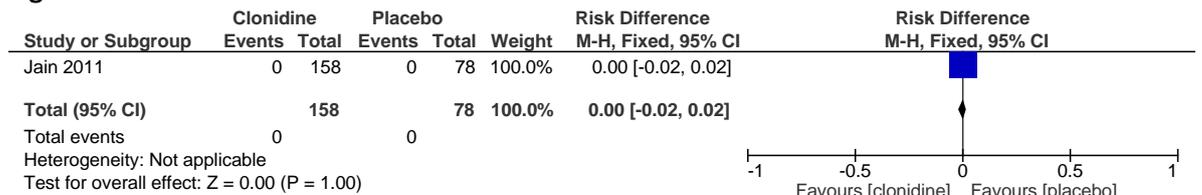


Figure 118: Serious adverse events at 16 weeks



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Clonidine versus methylphenidate

Figure 119: ADHD total symptoms teacher rated (Conners ASQ-T total score) at 16 weeks; 0-20, low values are beneficial

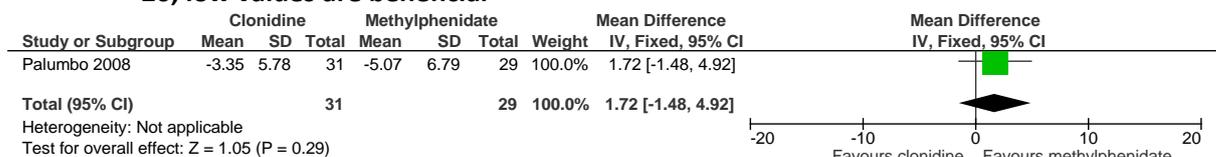
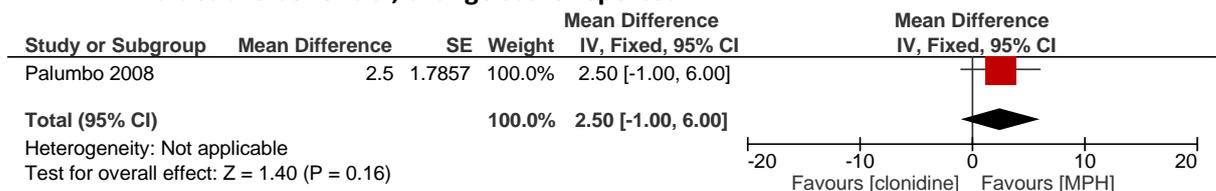
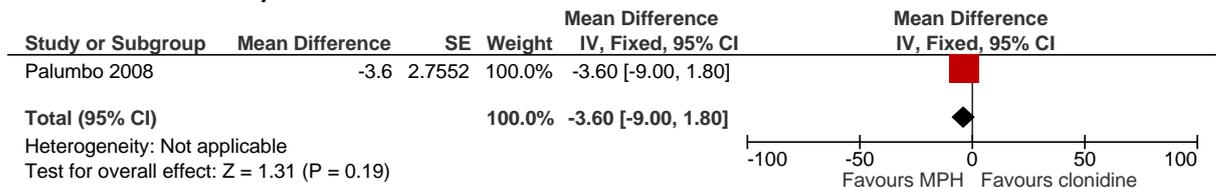


Figure 120: ADHD total symptoms parent rated (Conners ASQ-P total score) at 16 weeks; 0-20, low values are beneficial, change score reported



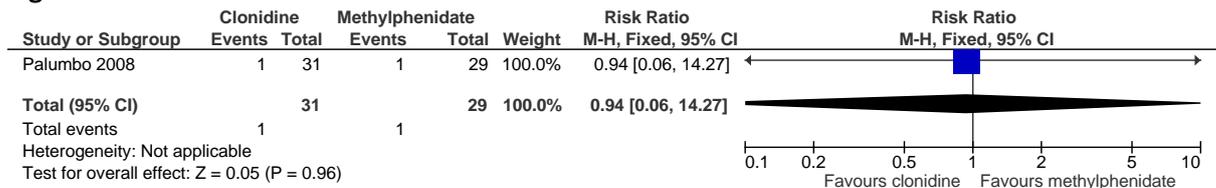
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Figure 121: Behaviour (Children's Global Assessment Scale at 16 weeks; 0-100, high values are beneficial)



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Figure 122: Discontinuation due to adverse events at 16 weeks

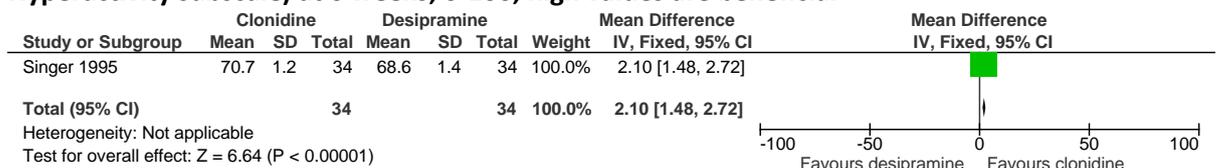


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Clonidine versus desipramine

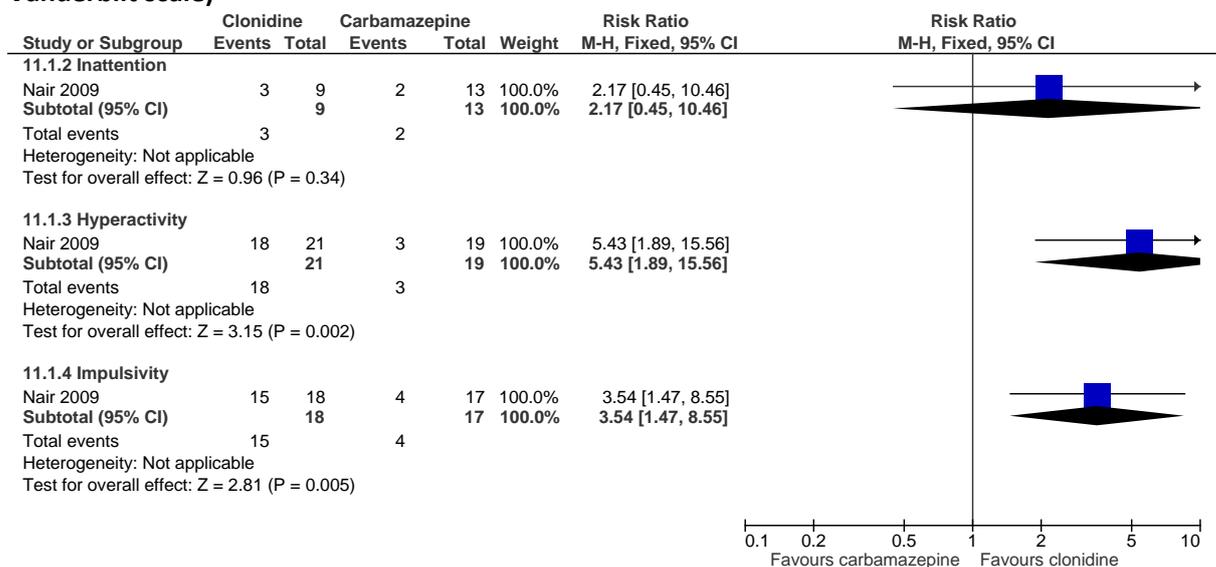
Figure 123: ADHD hyperactivity symptoms parent/teacher rated (Mother/Teacher CBCL Hyperactivity subscale) at 6 weeks; 0-100, high values are beneficial



4

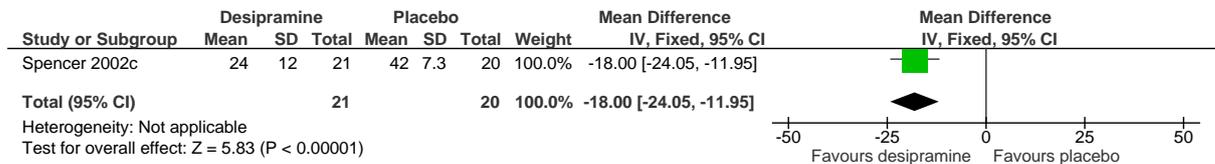
Clonidine versus carbamazepine

Figure 124: Treatment response at 4 weeks investigator rated (25% improvement on the Vanderbilt scale)



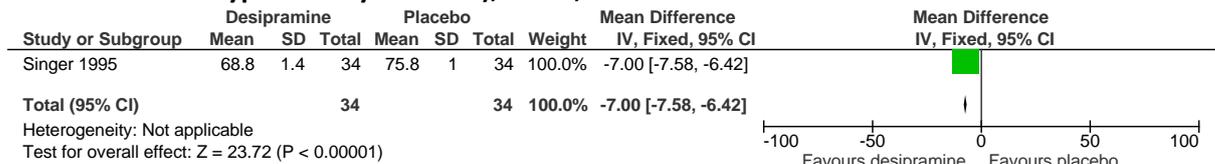
1 **Desipramine versus placebo**

Figure 125: ADHD total symptoms investigator rated at 9 weeks (ADHD-RS total scores); 0-54, low values are beneficial



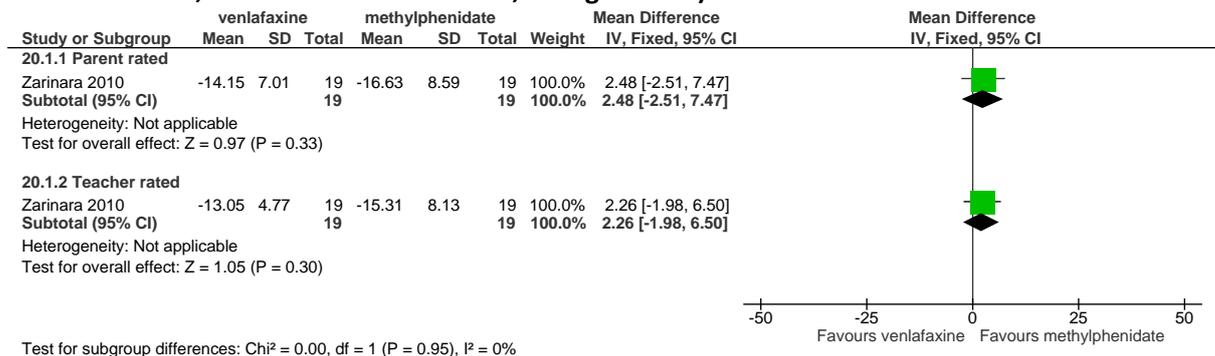
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Figure 126: ADHD hyperactivity symptoms at 6 weeks parent/teacher rated (Mother/Teacher CBCL Hyperactivity subscale), 0-100, low values are beneficial



3 **Venlafaxine versus methylphenidate**

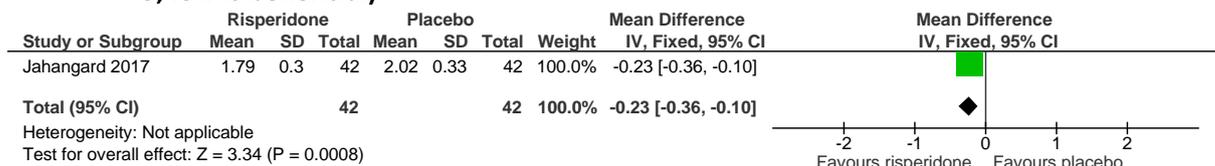
Figure 127: ADHD total symptoms parent and teacher rated at 6 weeks (ADHD-RS total score; 0-54; low values are beneficial, change scores)



4

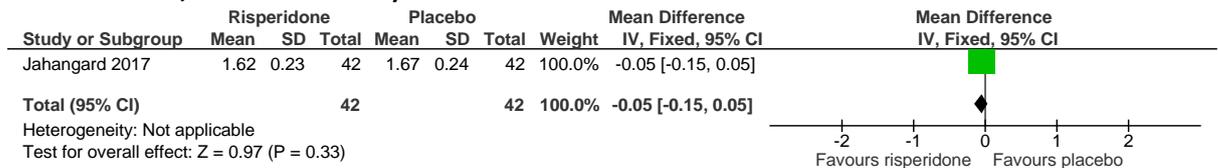
5 **Risperidone versus placebo**

Figure 128: ADHD inattention symptoms (8 weeks PT; parent rated; CPRS inattention subscale; 0-3; low is beneficial)



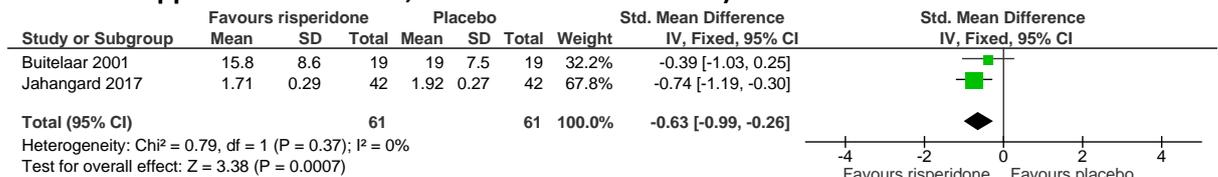
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Figure 129: ADHD hyperactivity symptoms (8 weeks PT; parent rated; CPRS hyperactivity subscale; 0-3; low is beneficial)



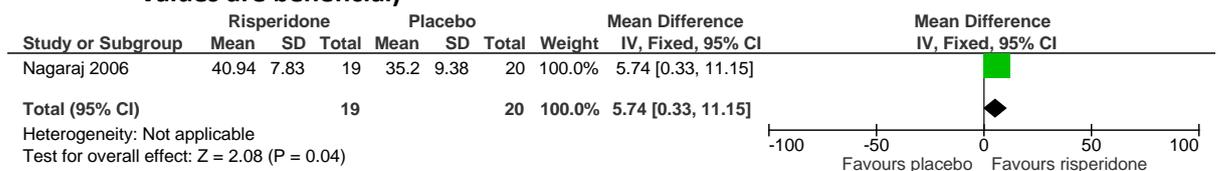
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Figure 130: Behaviour outcomes at 8 to 10 weeks (Aberrant Behaviour Checklist and CPRS oppositional subscale; low values are beneficial)



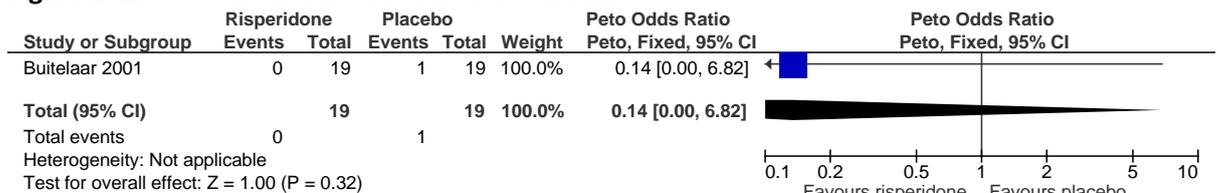
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Figure 131: Behaviour outcomes at 24 weeks (Children's Global Assessment Scale; 0-100; high values are beneficial)



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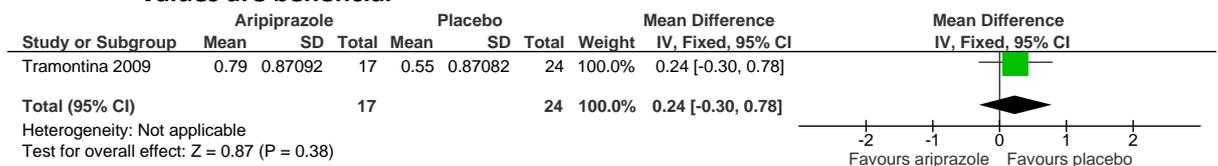
Figure 132: Serious adverse events at 6 weeks



4

Aripiprazole versus placebo

Figure 133: ADHD total symptoms parent rated at 6 weeks (SNAP-IV total scores); 0-3; lower values are beneficial

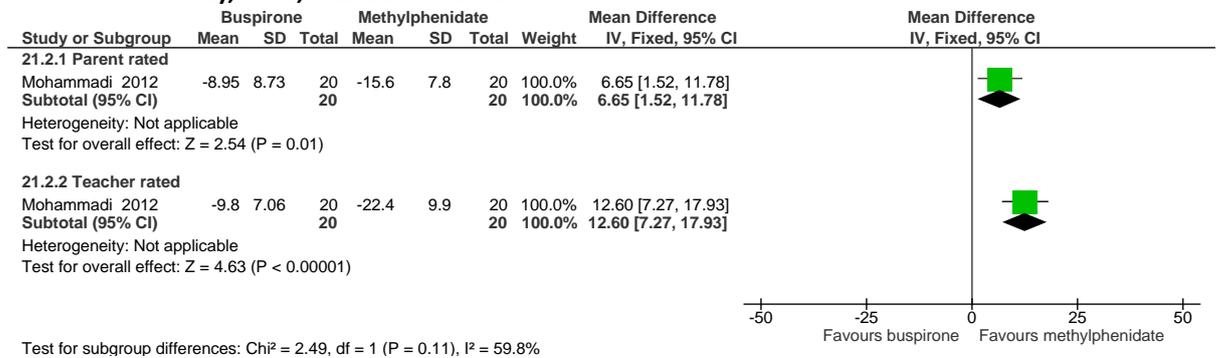


1 **Buspirone versus methylphenidate**

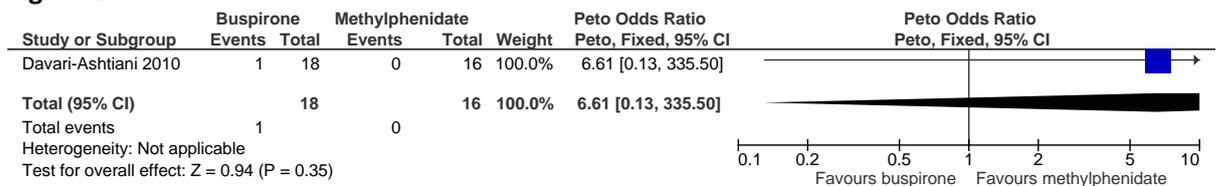
Figure 134: Treatment response at 6 weeks (more than 30% reduction in ADHD-RS total scores)



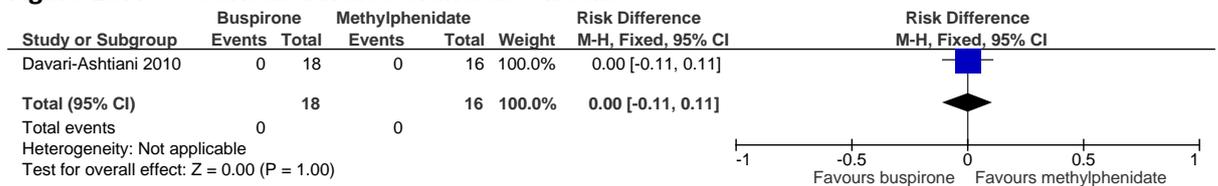
2 **Figure 135: ADHD total symptoms parent and teacher rated at 6 weeks (ADHD-RS total scores); 0-54; low values are beneficial**



3 **Figure 136: Discontinuation due to adverse events at 6 weeks**

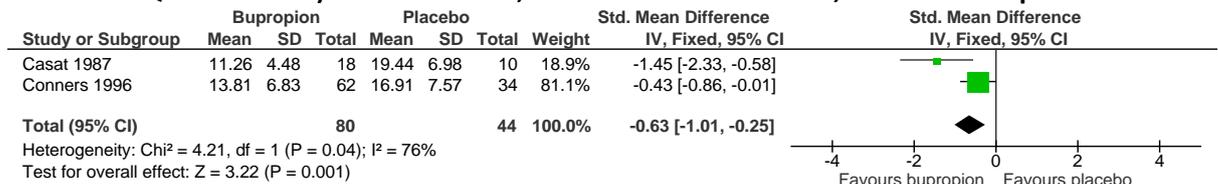


4 **Figure 137: Serious adverse events at 6 weeks**



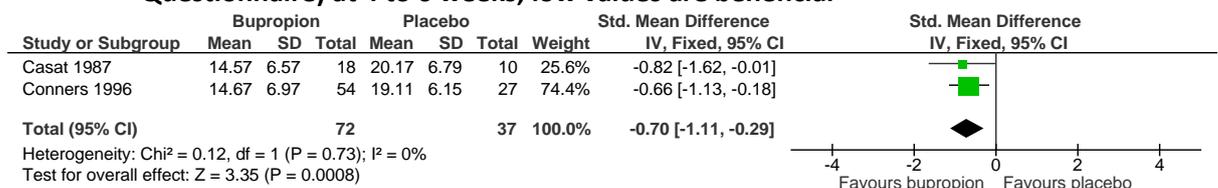
1 **Bupropion versus placebo**

Figure 138: ADHD total symptoms parent rated (CPTQ-P and Conners Abbreviated Parent Questionnaire) at 4 to 6 weeks; low values are beneficial, final values reported



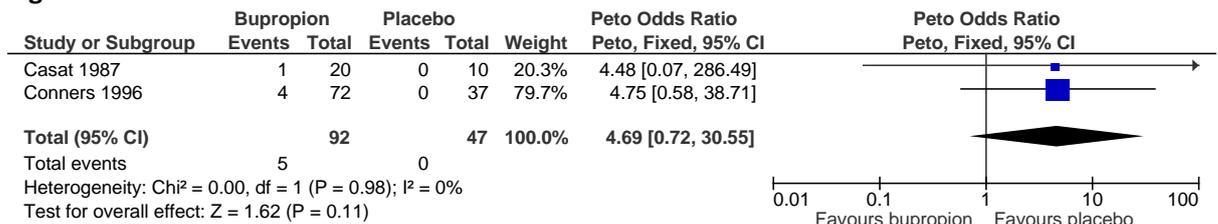
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Figure 139: ADHD total symptoms teacher rated (CPTQ-T and Conners Abbreviated Teacher Questionnaire) at 4 to 6 weeks; low values are beneficial



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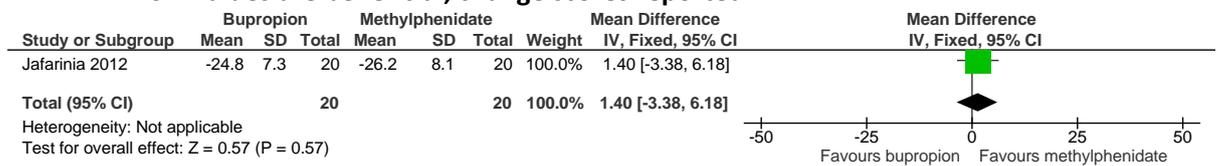
Figure 140: Discontinuation due to adverse events at 4 to 6 weeks



4

5 **Bupropion versus methylphenidate**

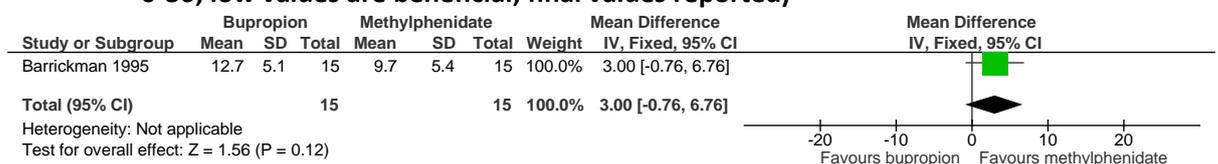
Figure 141: ADHD total symptoms parent rated at 6 weeks PT (ADHD-RS total scores); 0-54; low values are beneficial; change scores reported



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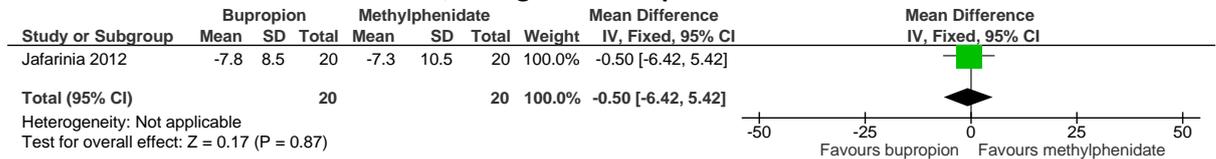
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Figure 142: ADHD total symptoms parent rated at 6 weeks crossover (IOWA conners rating scale; 0-30; low values are beneficial; final values reported)



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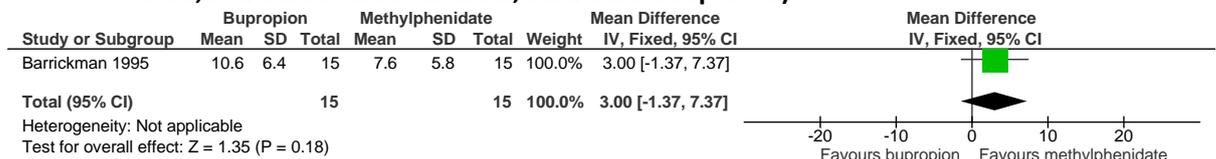
Figure 143: ADHD total symptoms teacher rated at 6 weeks PT (ADHD-RS total scores); 0-54; low values are beneficial; change scores reported



2

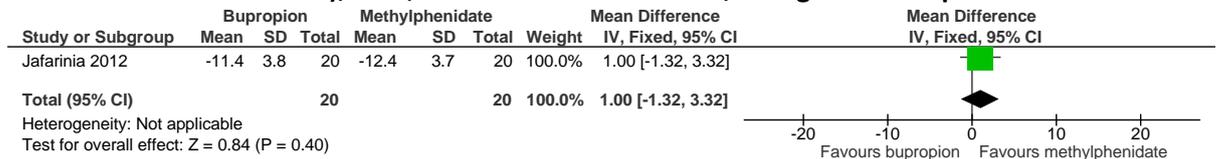
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Figure 144: ADHD total symptoms teacher rated at 6 weeks crossover (IOWA conners rating scale; 0-30; low values are beneficial; final values reported)



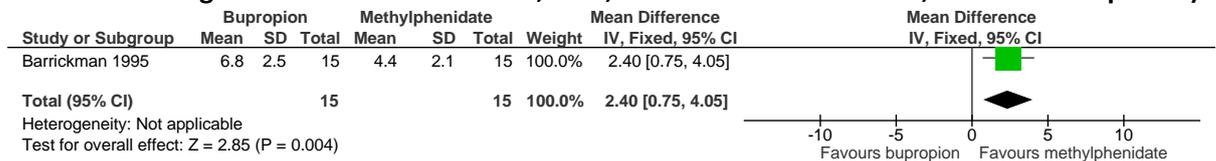
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Figure 145: ADHD inattention symptoms parent rated at 6 weeks PT (ADHD-RS inattention subscale scores); 0-27; low values are beneficial, change scores reported



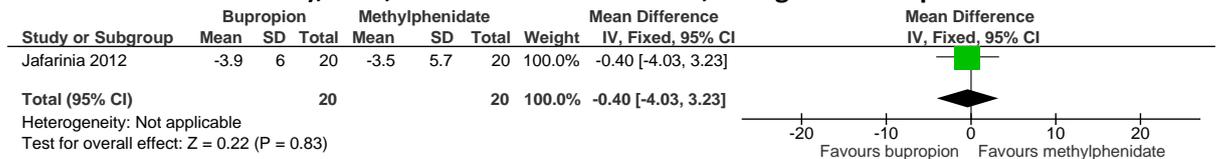
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Figure 146: ADHD inattention symptoms parent rated at 6 weeks crossover (IOWA conners rating scale inattention subscale; 0-15; low values are beneficial, final values reported)



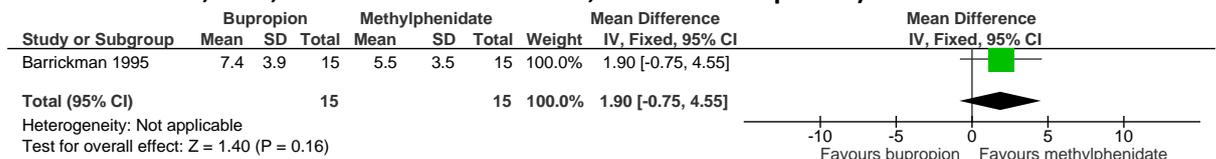
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Figure 147: ADHD inattention symptoms at 6 weeks PT (ADHD-RS inattention subscale scores teacher rated); 0-27; low values are beneficial; change scores reported



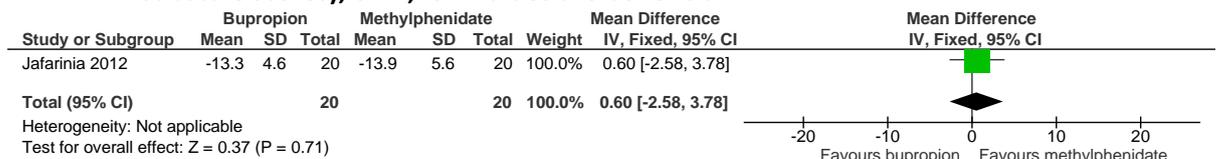
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Figure 148: ADHD inattention symptoms teacher rated at 6 weeks crossover (IOWA conners rating scale; 0-15; low values are beneficial; final values reported)



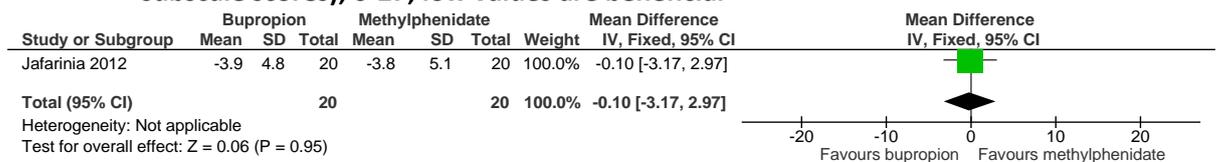
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Figure 149: ADHD hyperactivity symptoms parent rated at 6 weeks (ADHD-RS hyperactivity subscale scores); 0-27; low values are beneficial



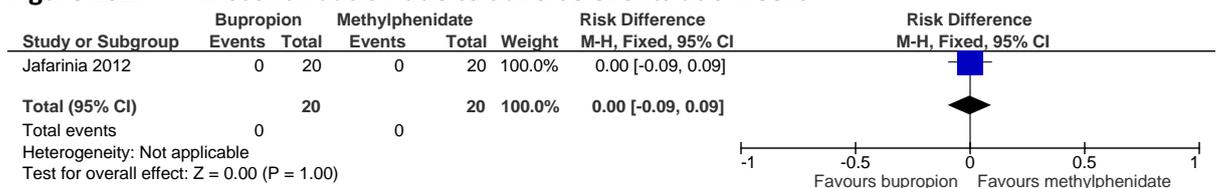
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Figure 150: ADHD hyperactivity symptoms teacher rated at 6 weeks (ADHD-RS hyperactivity subscale scores); 0-27; low values are beneficial



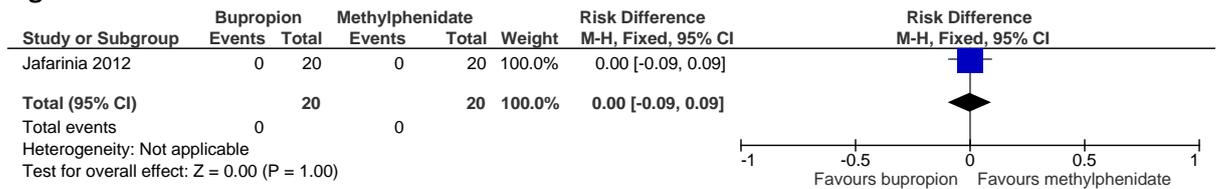
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Figure 151: Discontinuation due to adverse events at 6 weeks



5

Figure 152: Serious adverse events at 6 weeks

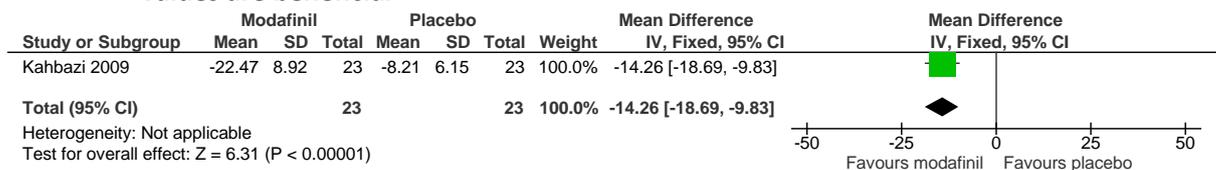


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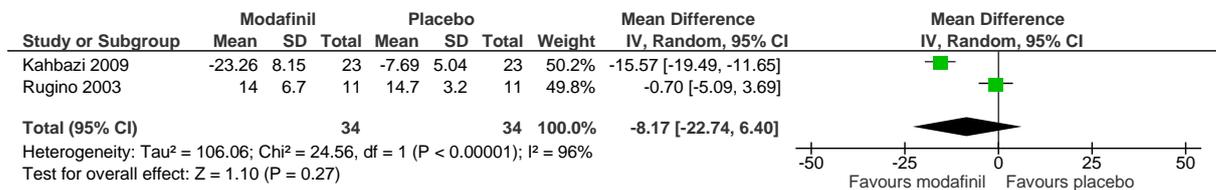
Modafinil versus placebo

Figure 153: ADHD total symptoms parent rated at 5 weeks (ADHD-RS total scores); 0-54; low values are beneficial



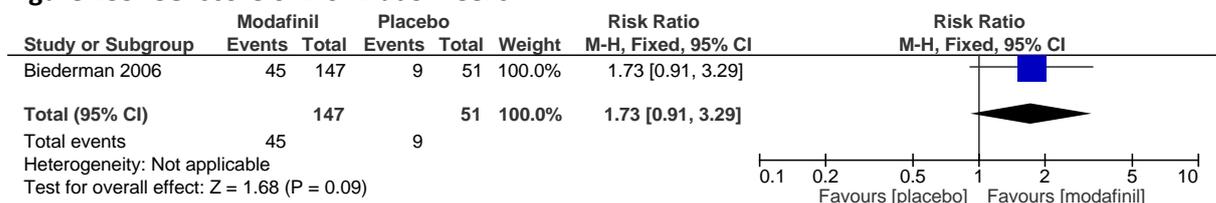
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Figure 154: ADHD total symptoms teacher rated at 5-6 weeks (ADHD-RS total scores); 0-54, lower values are beneficial



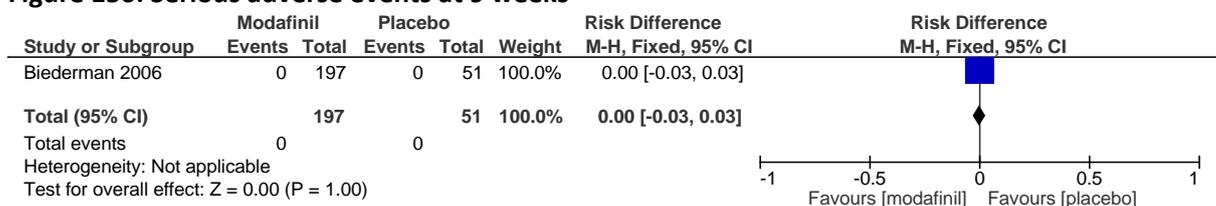
4

Figure 155: CGI score of 1 or 2 at 9 weeks



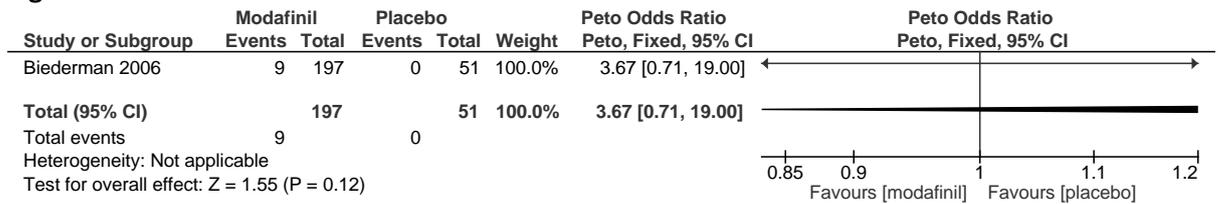
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Figure 156: Serious adverse events at 9 weeks



1

Figure 157: Discontinuation due to adverse events at 9 weeks



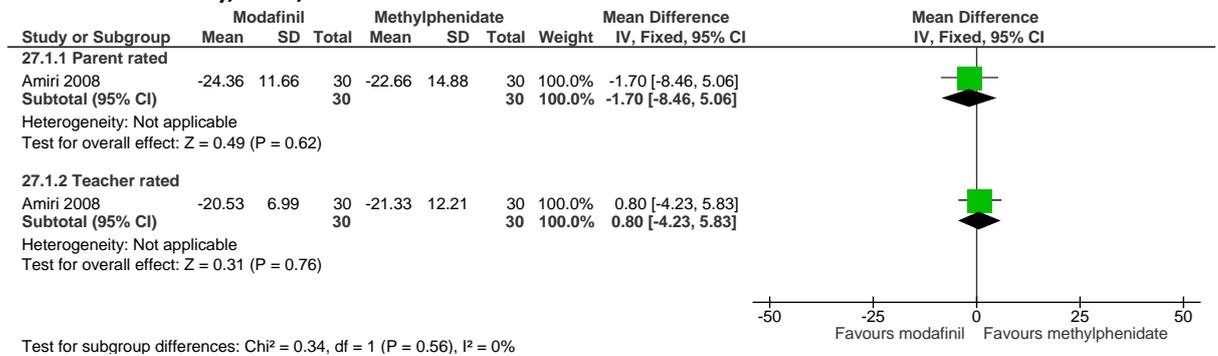
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4

Modafinil versus methylphenidate

Figure 158: ADHD total symptoms parent and teacher rated at 6 weeks (ADHD-RS total scores); 0-54; low scores are beneficial

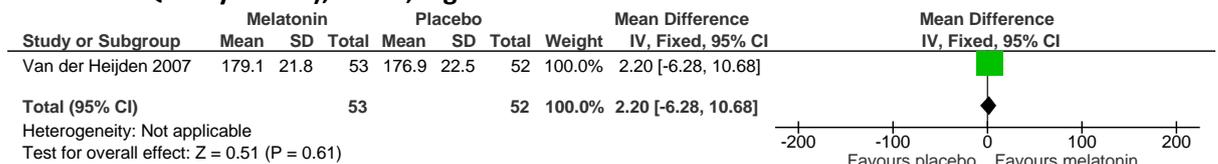


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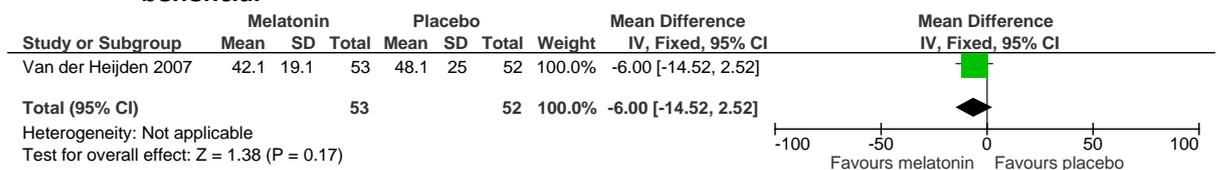
Melatonin versus placebo

Figure 159: Quality of Life at 4 weeks (TNO-AZL Questionnaire for Children's Health-Related Quality of Life), 0-224; higher values are beneficial



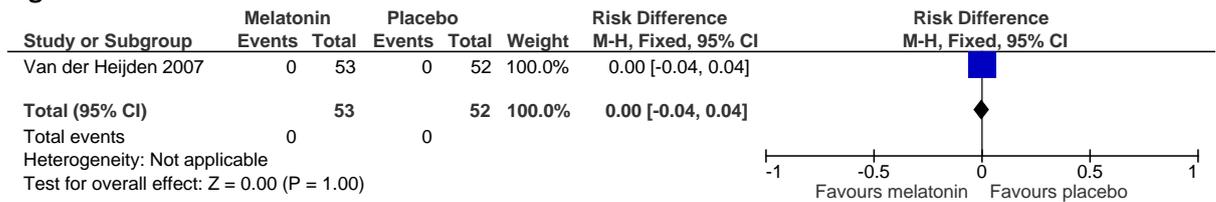
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Figure 160: Behavioural outcomes at 4 weeks (Teachers Report Form); 0-100; lower values are beneficial



8

Figure 161: Discontinuation due to adverse events at 4 weeks

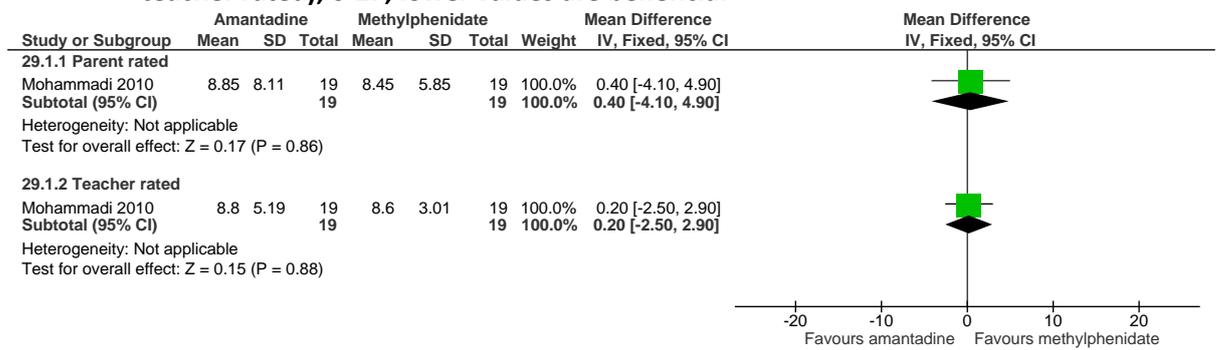


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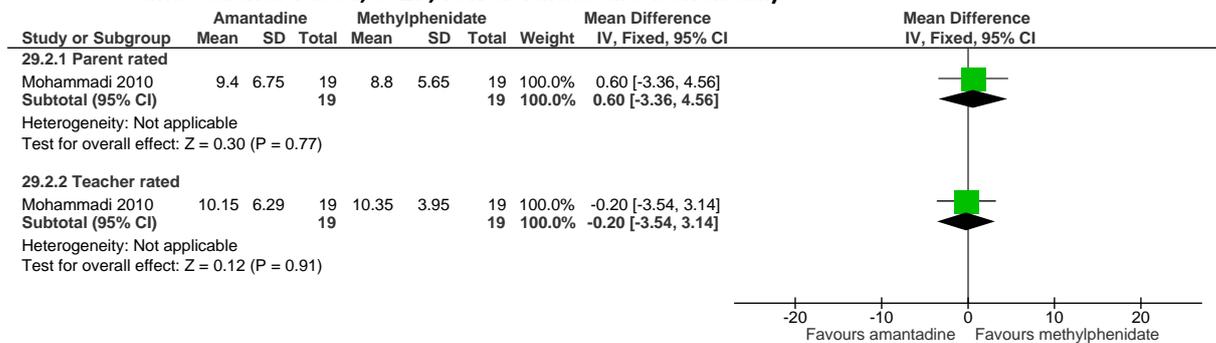
Amantadine versus methylphenidate

Figure 162: ADHD inattention symptoms at 6 weeks (ADHD-RS inattention subscale - Parent and teacher rated); 0-27, lower values are beneficial



3

Figure 163: ADHD hyperactivity symptoms at 6 weeks (ADHD-RS hyperactivity subscale – Parent and teacher rated; 0-27, lower values are beneficial)

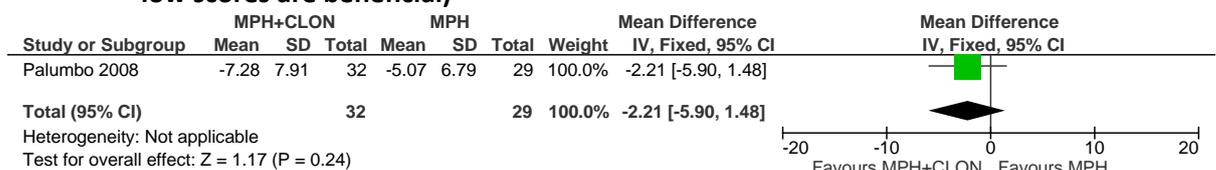


4

5

Methylphenidate and clonidine versus methylphenidate

Figure 164: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total scores; 0-20; low scores are beneficial)



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Figure 165: ADHD total symptoms parent rated at 16 weeks (Conners ASQ-P total scores; 0-20; low scores are beneficial)

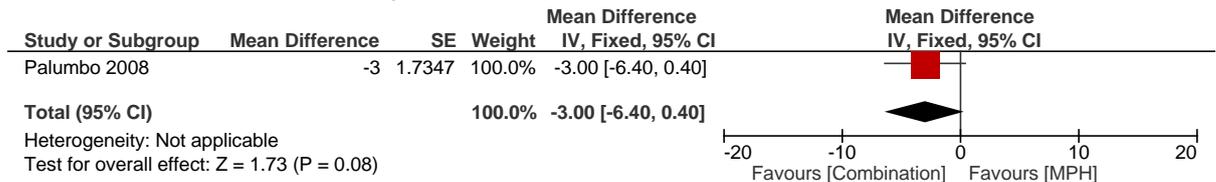
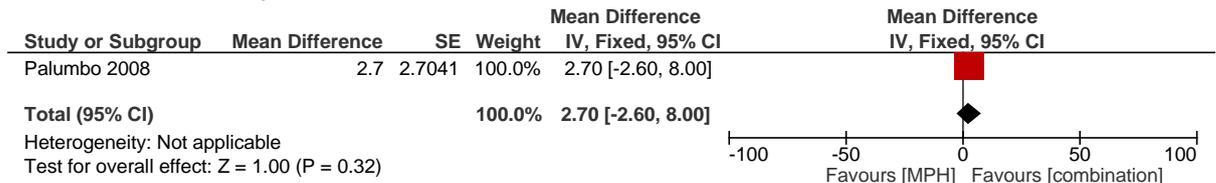
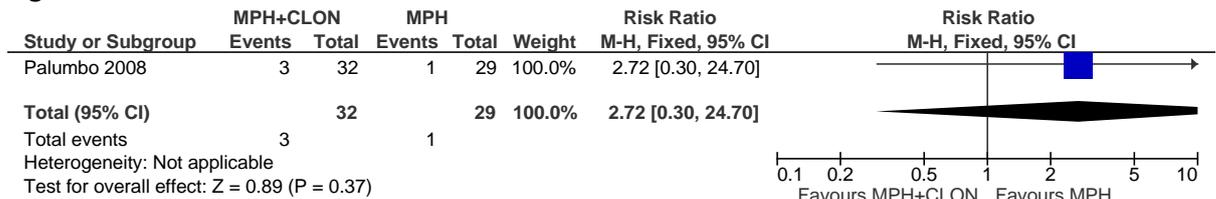


Figure 166: Behaviour at 16 weeks (Childrens global assessment scale; 0-100; high scores are beneficial)



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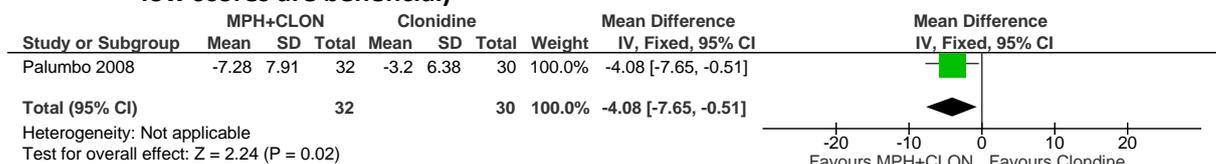
Figure 167: Discontinuation due to adverse events at 16 weeks



2

Methylphenidate and clonidine versus clonidine

Figure 168: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total scores; 0-20; low scores are beneficial)



3

Figure 169: Behaviour at 16 weeks (Childrens global assessment scale; 0-100; high scores are beneficial)

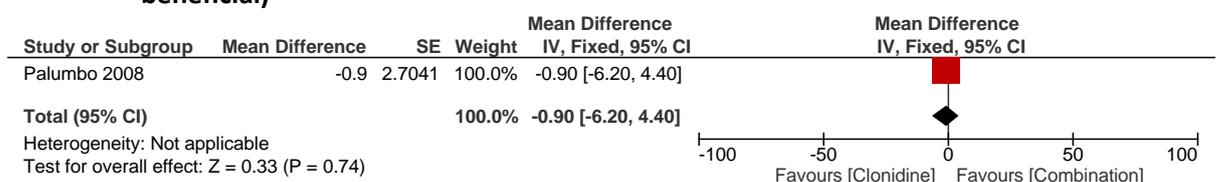
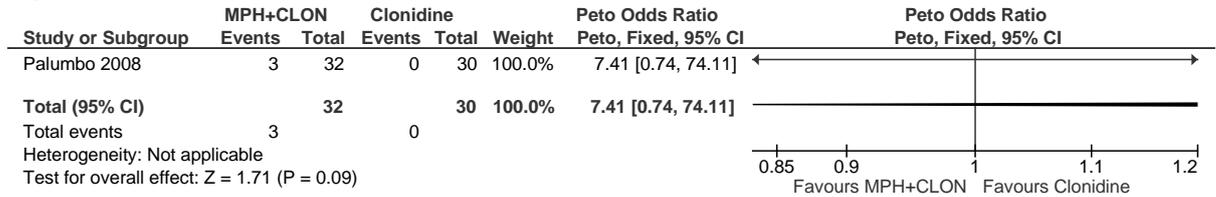


Figure 170: Discontinuation due to adverse events at 16 weeks

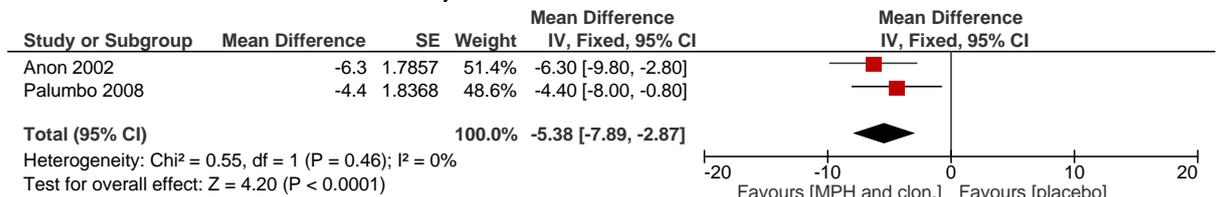


1

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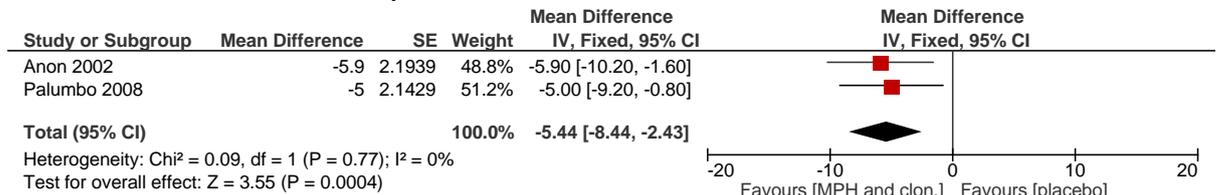
Methylphenidate and clonidine versus placebo

Figure 171: ADHD total symptoms teacher rated at 16 weeks (Conners ASQ-T total scores; 0-20; low scores are beneficial)



3

Figure 172: ADHD total symptoms parent rated at 16 weeks (Conners ASQ-P total scores; 0-20; low scores are beneficial)



4

Figure 173: Behaviour at 16 weeks (Childrens global assessment scale; 0-100; high scores are beneficial)

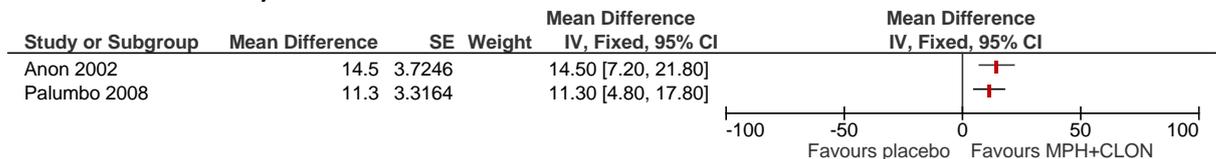
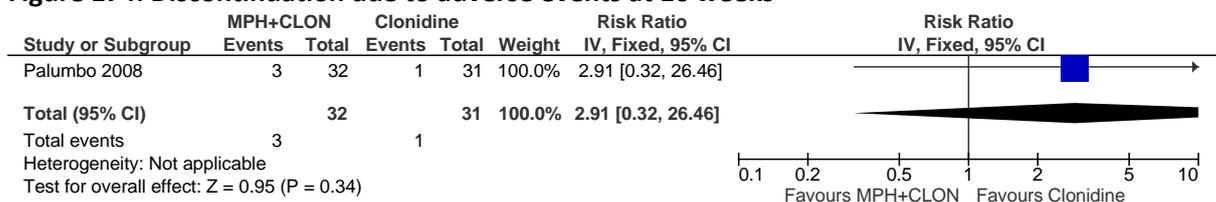
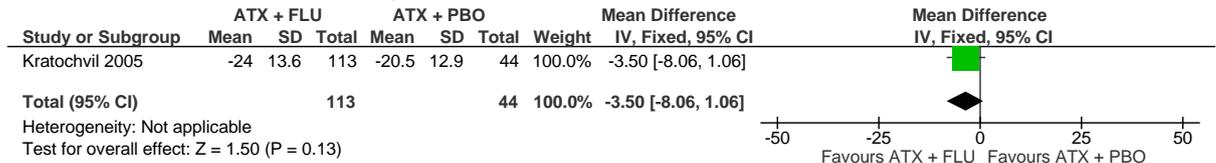


Figure 174: Discontinuation due to adverse events at 16 weeks



1 **Amotoxetine and fluoxetine versus atomoxetine and placebo**

Figure 175: ADHD total symptoms investigator rated (8 weeks; ADHD-RS total scores; 0-54; low scores are beneficial)



2

Figure 176: ADHD inattention symptoms investigator rated (8 weeks; ADHD-RS inattention subscale scores; 0-27; low scores are beneficial)

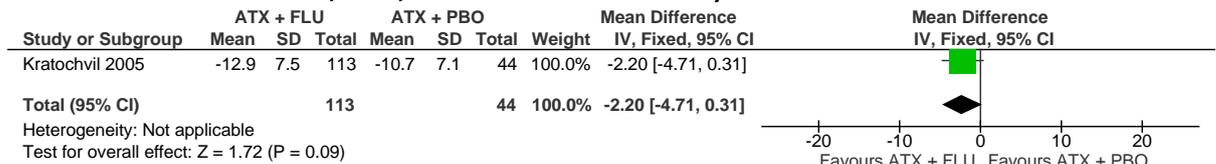
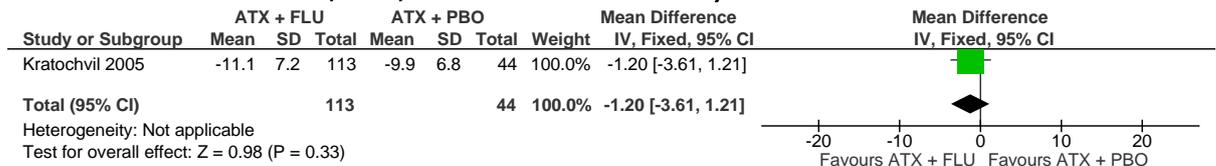
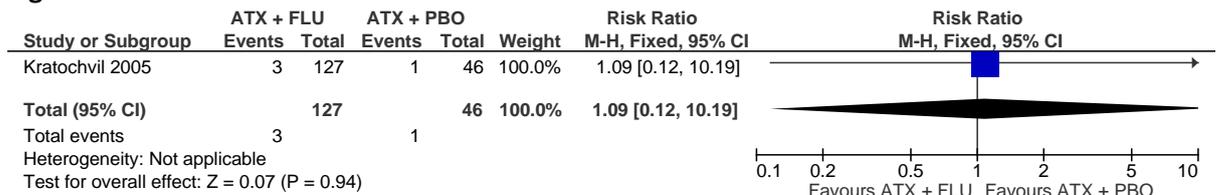


Figure 177: ADHD hyperactivity symptoms investigator rated (8 weeks; ADHD-RS hyperactivity subscale scores; 0-27; low scores are beneficial)



3

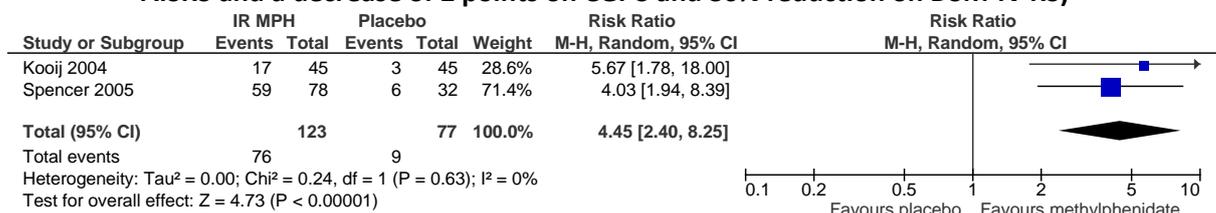
Figure 178: Discontinuation due to adverse events at 8 weeks



4 **E.1.3 Adults**

5 **Immediate release methylphenidate versus placebo**

Figure 179: Treatment response at 3-6 weeks (defined as CGI of 1 or 2 and 30% decrease on AISRS and a decrease of 2 points on CGI-S and 30% reduction on DSM-IV RS)



1

Figure 180: ADHD total symptoms investigator rated (CAARS and Barkleys ADHD Rating Scale total scores at 3-4 weeks; final values reported; lower values are beneficial)

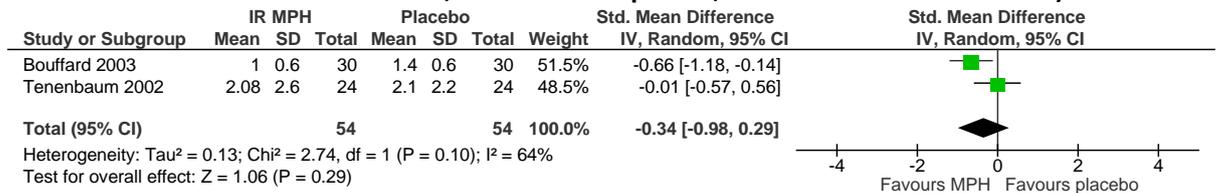
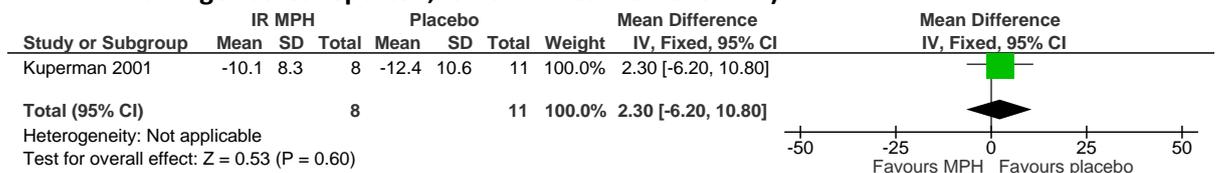


Figure 181: ADHD total symptoms investigator rated (ADHD-RS total scores at 7 weeks; 0-54, change scores reported; lower values are beneficial)



2

Figure 182: CGI-I score of 1 or 2 at 7 weeks

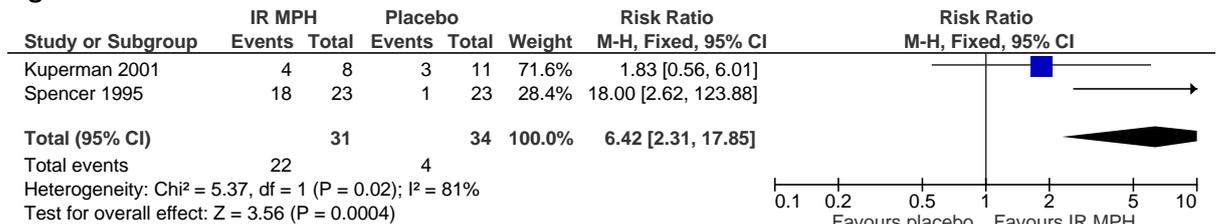
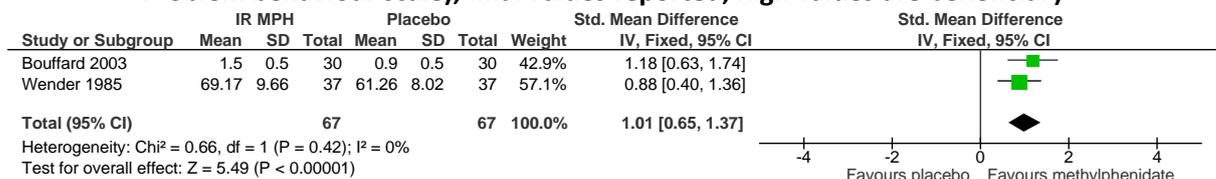
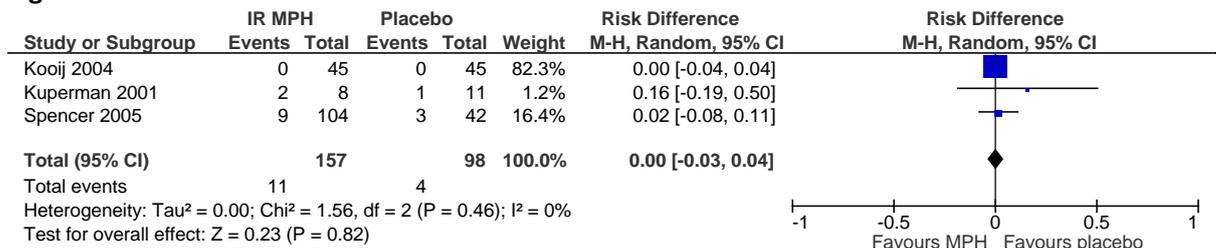


Figure 183: Behaviour outcome at 2 to 4 weeks (Global assessment of functioning and Problem behaviour scale); final values reported; high values are beneficial)



3

Figure 184: Discontinuation due to adverse events at 3-7 weeks



1

OROS release methylphenidate versus placebo

Figure 185: Treatment response (defined as CGI-I score of 1 or 2 and 30% reduction on AISRS and 30% reduction on WRAADDs) at 6-8 weeks

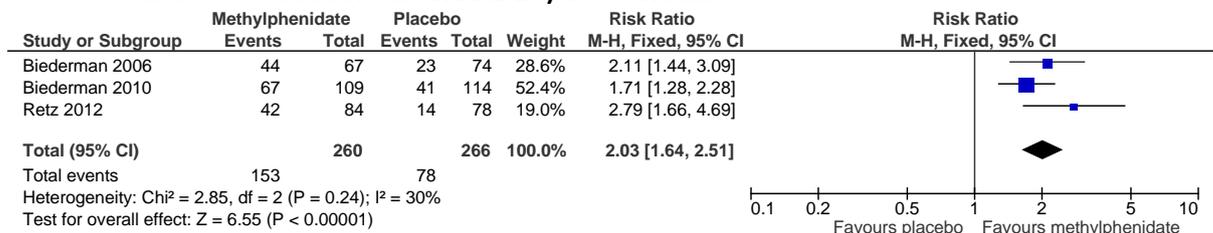
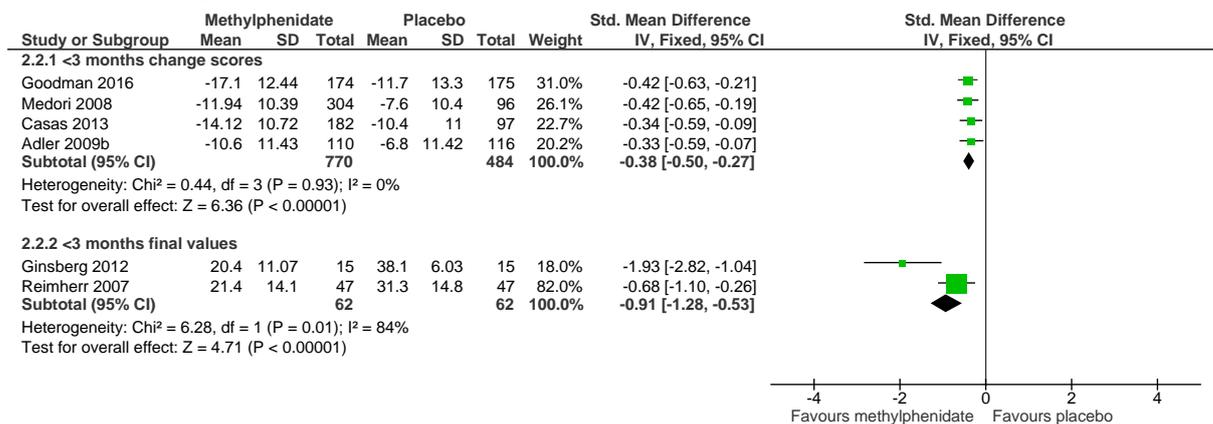


Figure 186: ADHD total symptoms investigator rated (multiple scales including CAARS-O:SV and ADHD-RS total scores) at 5 to 13 weeks; low values are beneficial, final values and change scores reported)



2

Figure 187: ADHD total symptoms self rated (CAARS-O:SV total scores and CAARS ADHD index) at 2 to 5 weeks; low values are beneficial, final values reported)

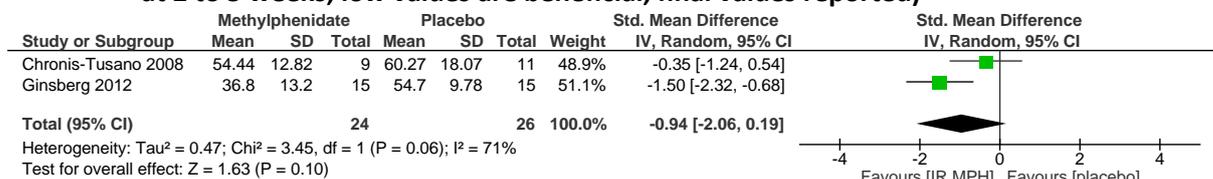


Figure 188: ADHD total symptoms self rated (CAARS total scores at 5 to 6 weeks; 0-71, low values are beneficial, change scores reported)

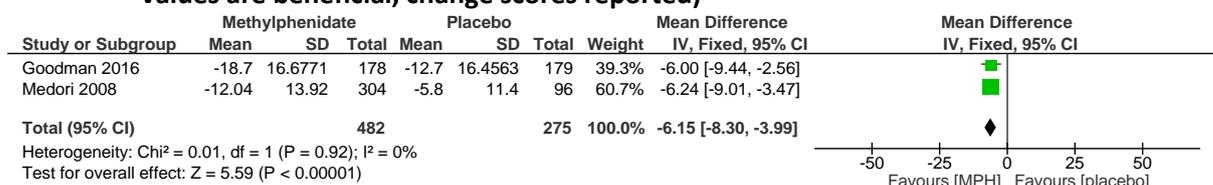
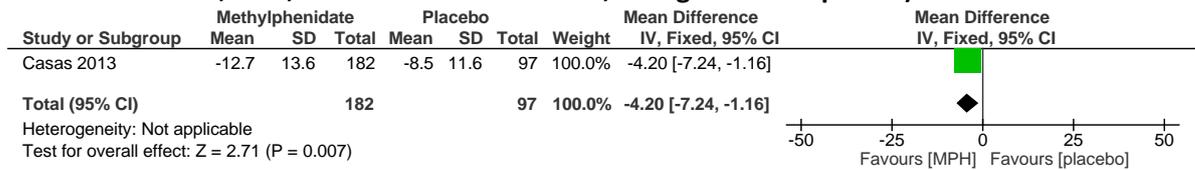
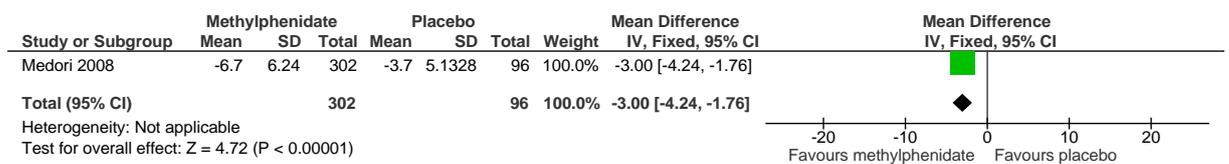


Figure 189: ADHD total symptoms self rated (CAARS self report form total scores at 13 weeks; 0-54, low values are beneficial, change scores reported)



1

Figure 190: ADHD inattention symptoms investigator rated (5 weeks; CAARS inattention subscale; 0-27, low values are beneficial, change scores reported)



4

Figure 191: ADHD inattention symptoms investigator rated (CAARS and ADHD-RS inattention subscales at 3 to 8 weeks; low values are beneficial, final values reported)

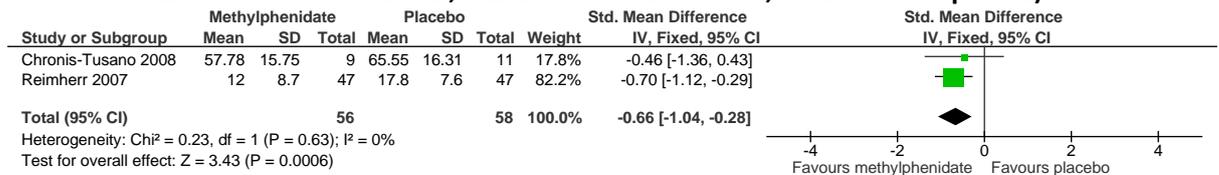
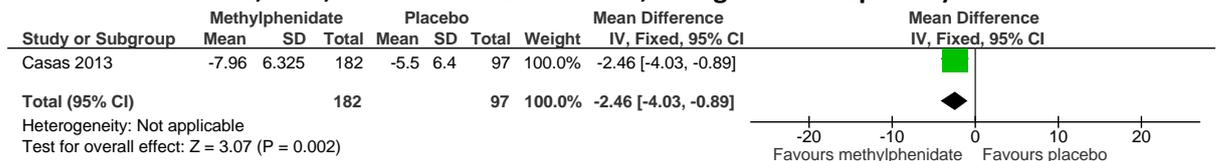


Figure 192: ADHD inattention symptoms investigator rated (CAARS inattention subscale scores at 13 weeks; 0-27, low values are beneficial, change scores reported)



5

Figure 193: ADHD hyperactivity symptoms investigator rated (CAARS hyperactive subscale at 5 weeks; 0-27, low values are beneficial, change scores reported)

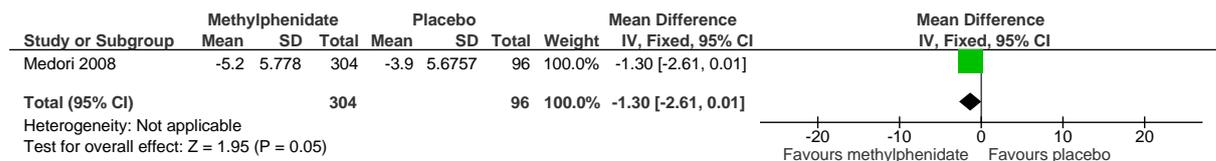


Figure 194: ADHD hyperactivity symptoms investigator rated (ADHD-RS and CAARS hyperactivity subscale) at 2 to 8 weeks; low values are beneficial, final values reported)

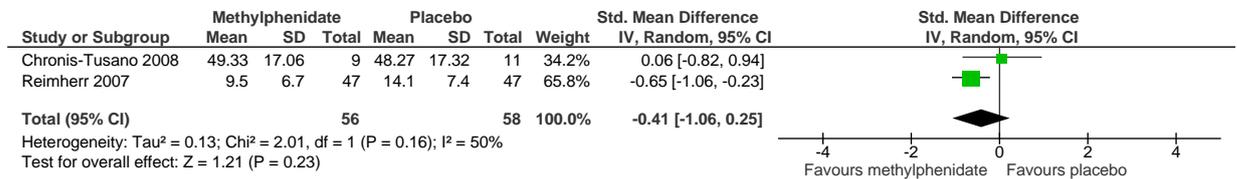


Figure 195: ADHD hyperactivity symptoms investigator rated (CAARS hyperactivity subscale) at 13 weeks; 0-27; low values are beneficial, change scores reported)

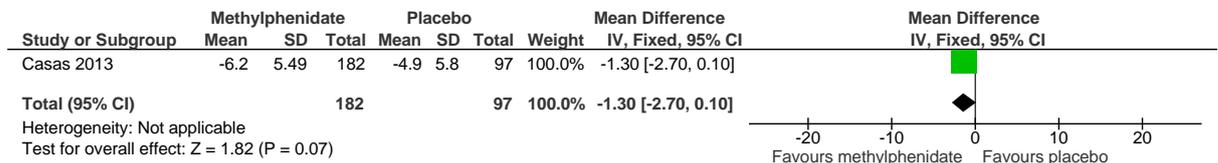


Figure 196: CGI-I score of 1 or 2 at 7-13 weeks

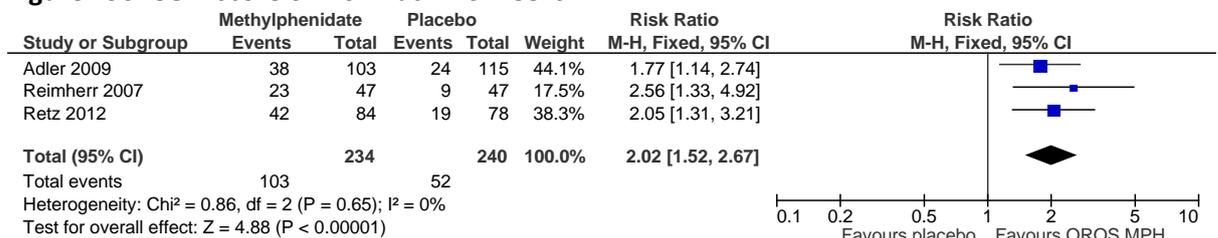
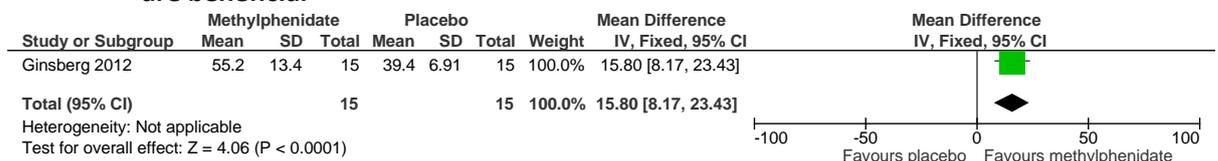
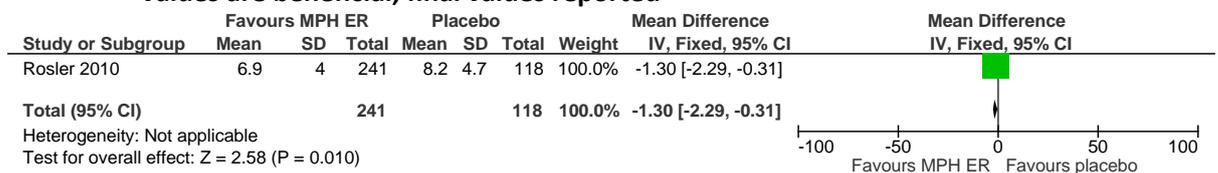


Figure 197: Behaviour outcome (Global Assessment of Functioning) at 5 weeks; 0-100; high values are beneficial



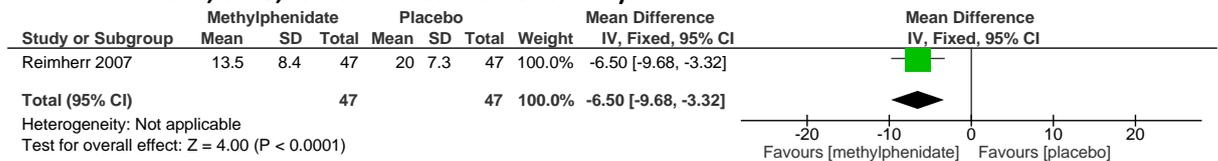
1

Figure 198: Emotional dysregulation (PT; CAARS-S:L Emotional lability scale) at 5 weeks; 0-12, low values are beneficial, final values reported



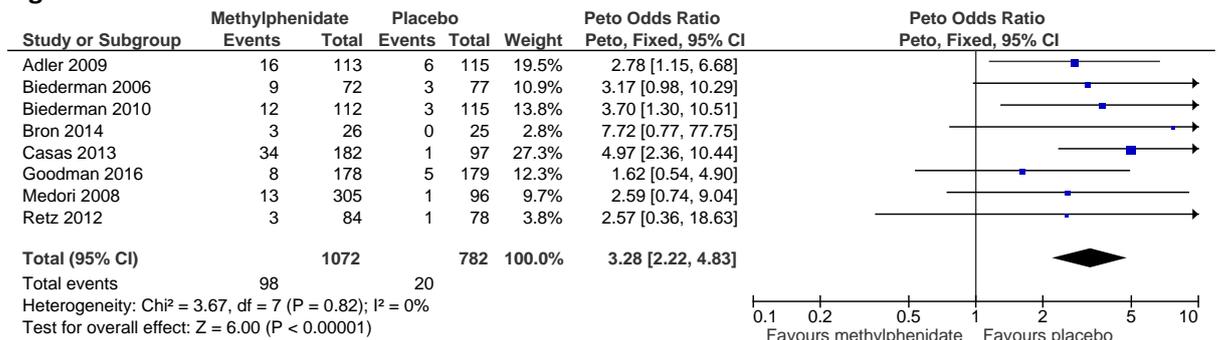
1

Figure 199: Emotional dysregulation at 4 weeks (Crossover trial; WRAADS emotional dysregulation score; 0-28; lower values are beneficial)



2

Figure 200: Discontinuation due to adverse events at 6 to 13 weeks

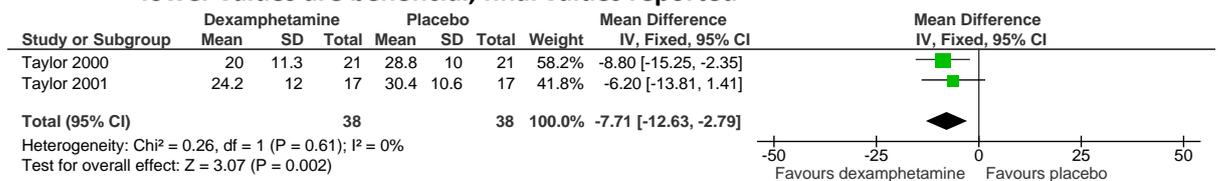


3

4

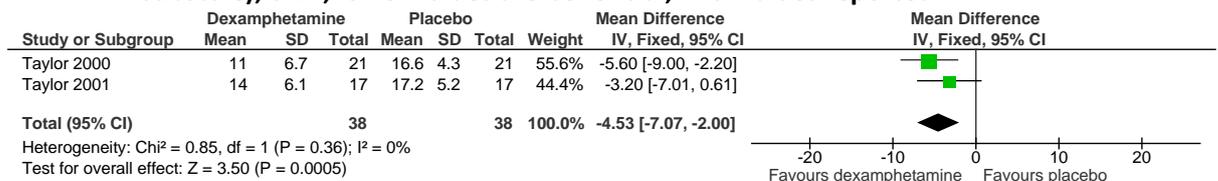
Dexamphetamine versus placebo

Figure 201: ADHD total symptoms investigator rated at 2 weeks (DSM-IV RS total scores); 0-54, lower values are beneficial, final values reported



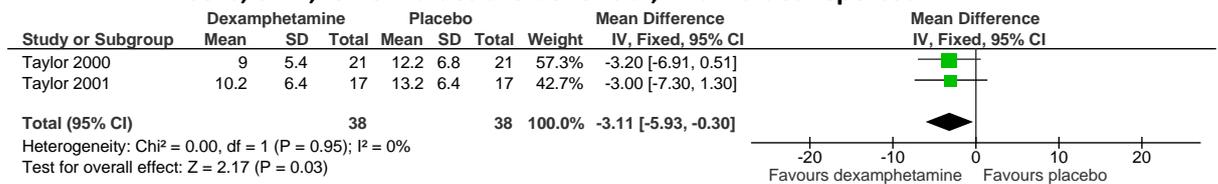
5

Figure 202: ADHD inattention symptoms investigator rated at 2 weeks (DSM-IV RS Inattentive subscale); 0-27, lower values are beneficial, final values reported



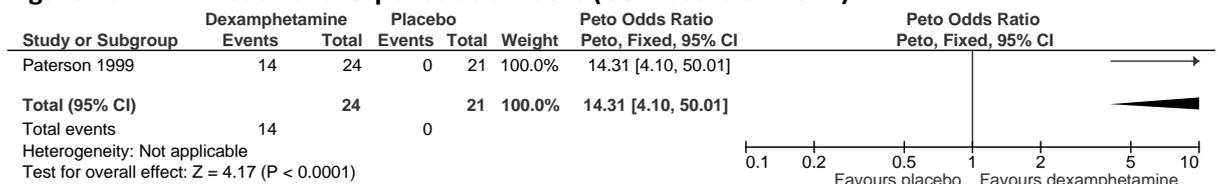
6

Figure 203: ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale) at 2 weeks; 0-27, lower values are beneficial, final values reported



1

Figure 204: Treatment response at 6 weeks (CGI-I score of 1 or 2)

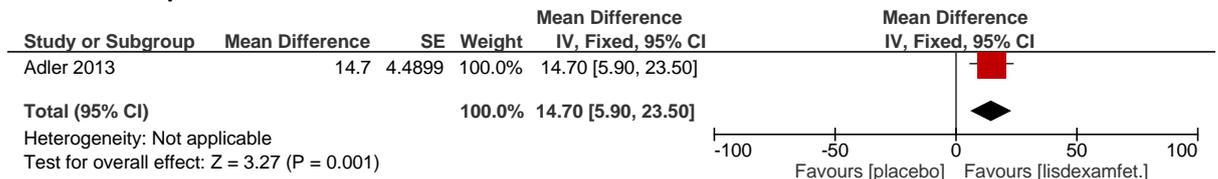


2

3

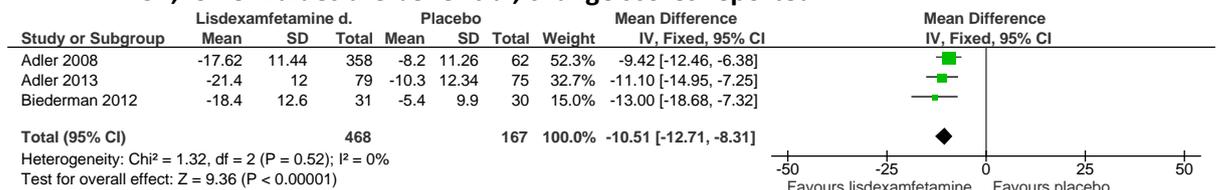
Lisdexamfetamine dimesylate versus placebo

Figure 205: Quality of life at 10 weeks (AAQoL), 0-100, high values are beneficial, change scores reported



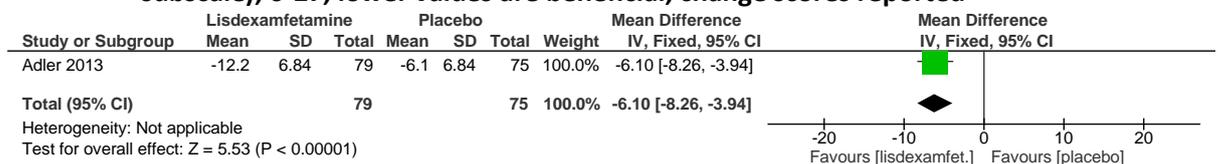
4

Figure 206: ADHD total symptoms investigator rated at 4 to 10 weeks (ADHD-RS total scores); 0-54, lower values are beneficial, change scores reported



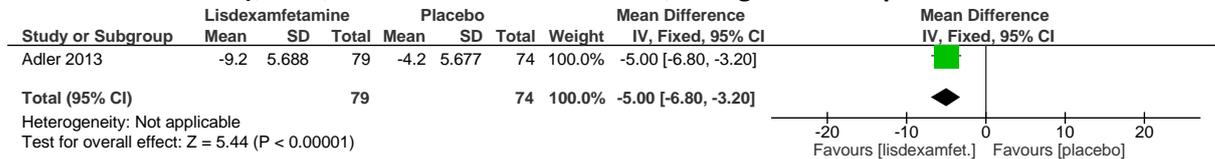
5

Figure 207: ADHD inattention symptoms investigator rated at 10 weeks (ADHD-RS inattention subscale); 0-27, lower values are beneficial, change scores reported



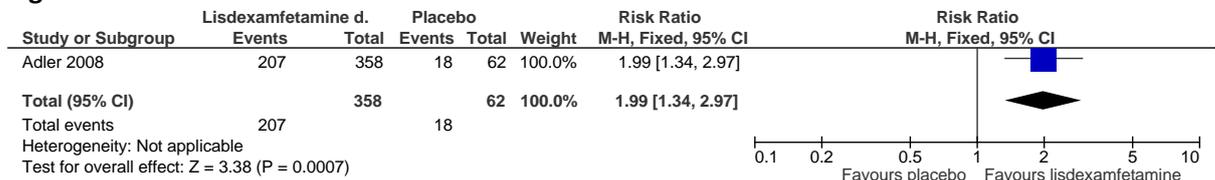
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Figure 208: ADHD hyperactivity symptoms investigator rated at 10 weeks (ADHD-RS hyperactivity subscale); 0-27, lower values are beneficial, change scores reported



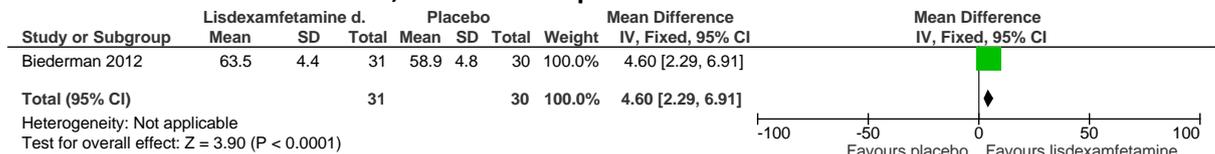
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Figure 209: CGI score of 1 or 2 at 4 weeks



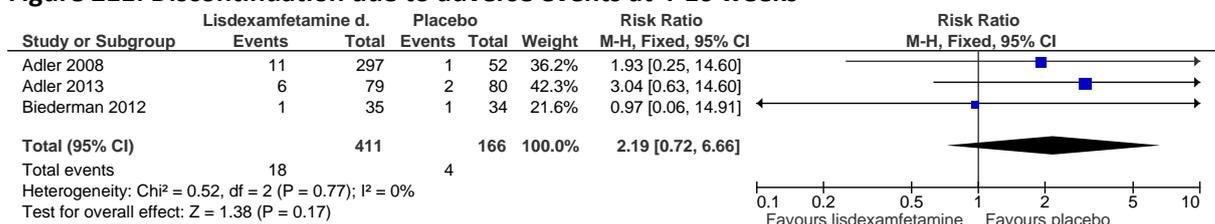
3

Figure 210: Behavioural outcomes at 6 weeks (Global assessment of functioning); 0-100, higher values are beneficial, final values reported



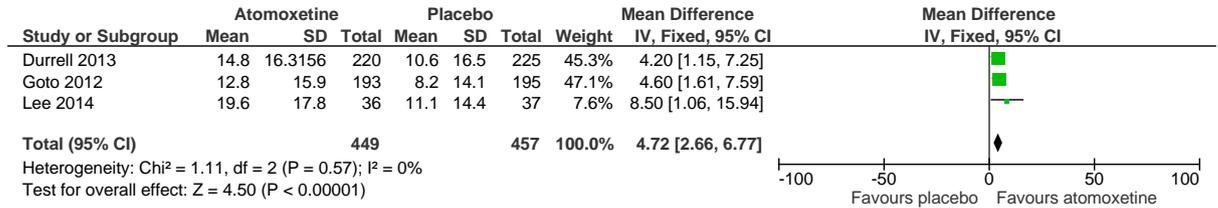
4

Figure 211: Discontinuation due to adverse events at 4-10 weeks



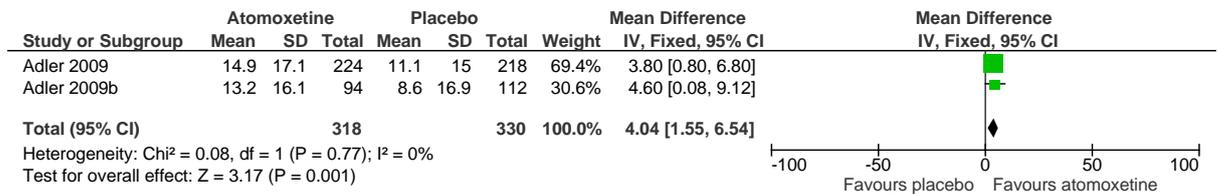
1 **Atomoxetine versus placebo**

Figure 212: Quality of Life at 10 to 12 weeks (AAQoL Total Scores); 0-100; high values are beneficial



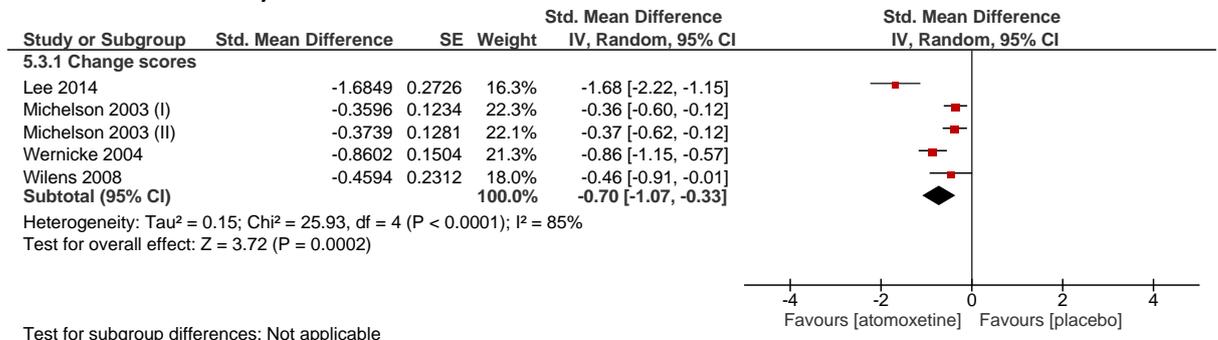
2

Figure 213: Quality of life at 16 to 24 weeks (AAQoL Total Scores); 0-100; high values are beneficial



3

Figure 214: ADHD total symptoms investigator rated at 8 to 12 weeks (multiple scales including AISRS and ADHD-RS total scores; change scores reported; low values are beneficial)



4

Figure 215: ADHD total symptoms investigator rated at 8 to 12 weeks (AISRS and CAARS total scores; 0-54; final values reported; low values are beneficial)

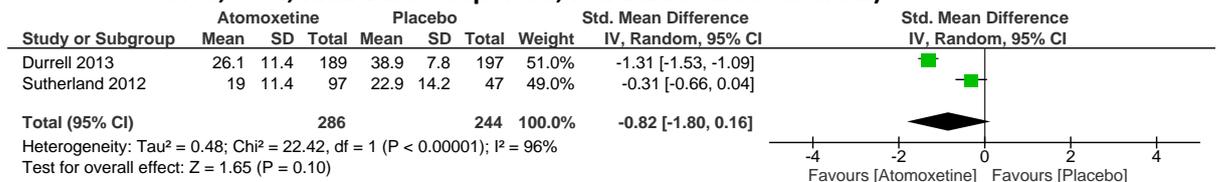
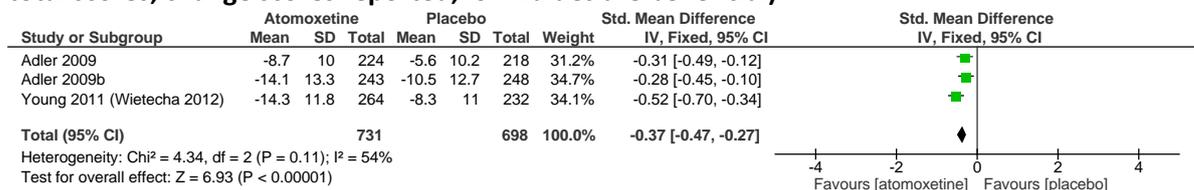
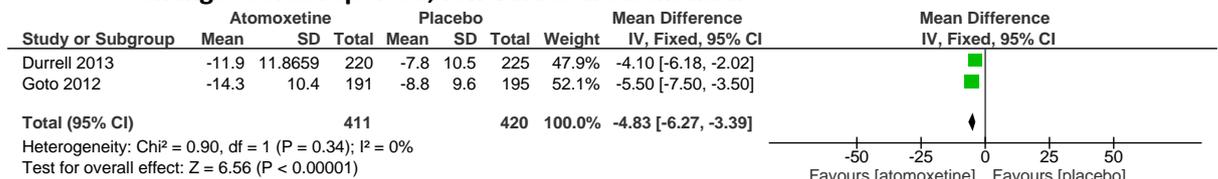


Figure 216: ADHD total symptoms investigator rated at 16 to 24 weeks (AISRS and CAARS total scores; change scores reported; low values are beneficial)



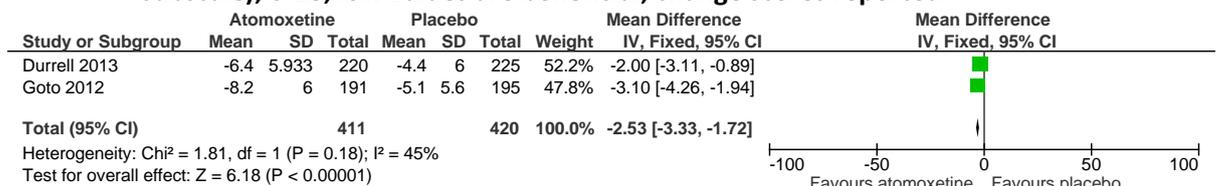
1

Figure 217: ADHD total symptoms self rated at 10 to 12 weeks (CAARS total score); 0-84 change scores reported; low values are beneficial



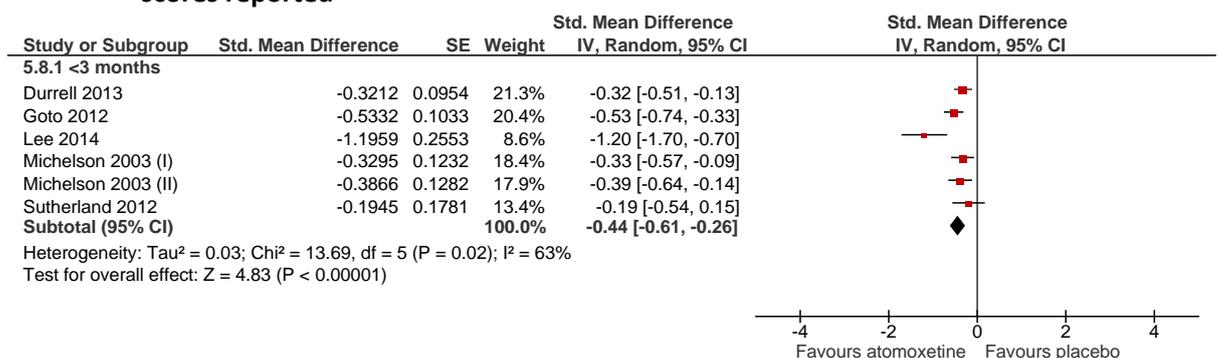
2

Figure 218: ADHD inattention symptoms self rated at 10 to 12 weeks (CAARS inattention subscale); 0-28; low values are beneficial; change scores reported



3

Figure 219: ADHD inattention symptoms investigator rated at 8 to 12 weeks (multiple scales including CAARS and ADHD-RS inattention subscales); low values are beneficial; change scores reported



1

Figure 220: ADHD inattention symptoms investigator rated at 16 to 24 weeks (multiple scales including AISRS and CAARS inattention subscale scores; change scores reported; low values are beneficial)

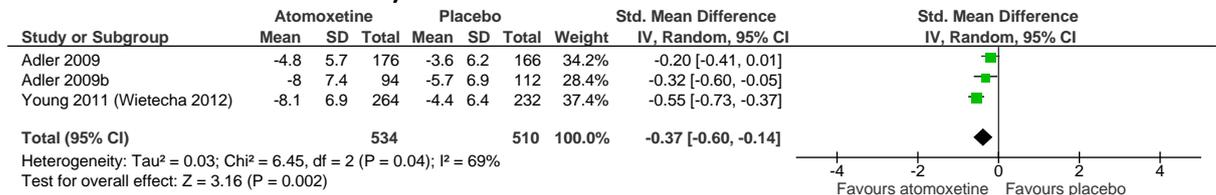
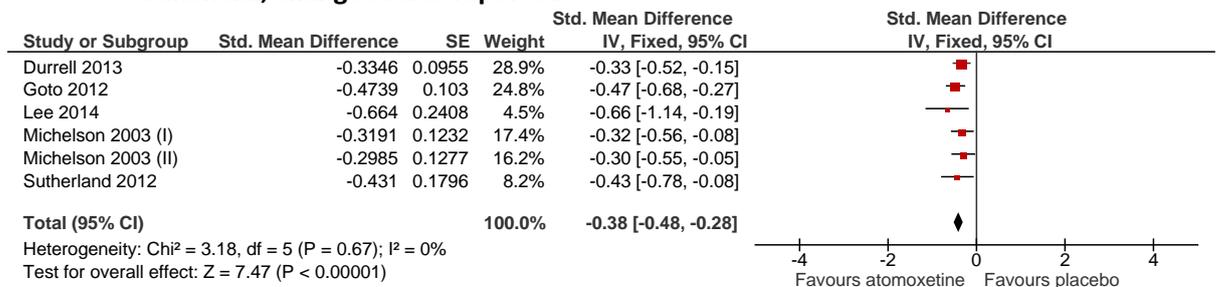


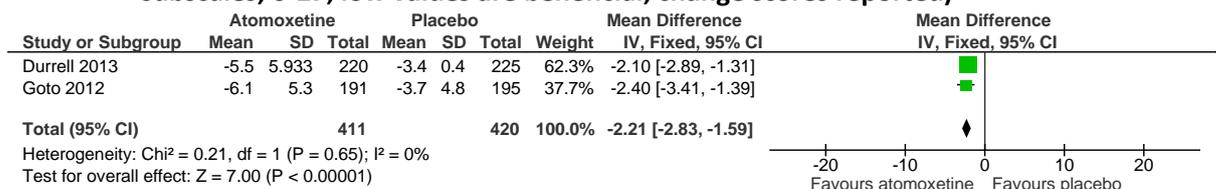
Figure 221: ADHD hyperactivity symptoms investigator rated at 8 to 12 weeks (multiple scales including AISRS and CAARS hyperactivity/impulsivity subscale); low values are beneficial; change scores reported



2

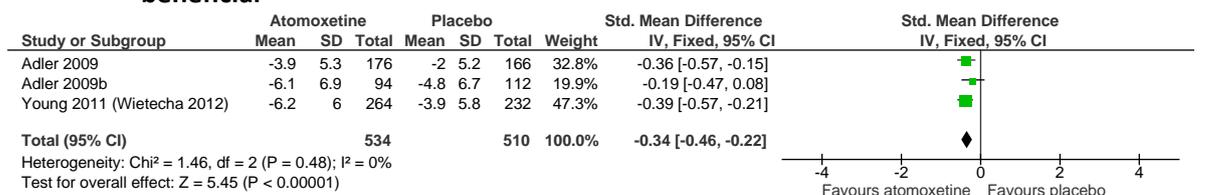
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Figure 222: ADHD hyperactivity symptoms self rated at 10 to 12 weeks (CAARS hyperactivity subscales; 0-27; low values are beneficial; change scores reported)



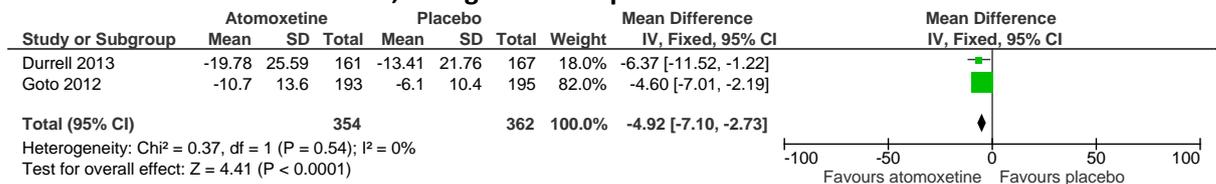
4

Figure 223: ADHD hyperactivity symptoms at 16 to 24 weeks investigator rated (CAARS and AISRS hyperactivity subscales); 0-27; change scores reported; low values are beneficial



5

Figure 224: Behaviour outcome at 10 to 12 weeks (BRIEF-A self report total score); 0-100, low values are beneficial, change scores reported



1

Figure 225: Discontinuation due to adverse events at 8 to 12 weeks

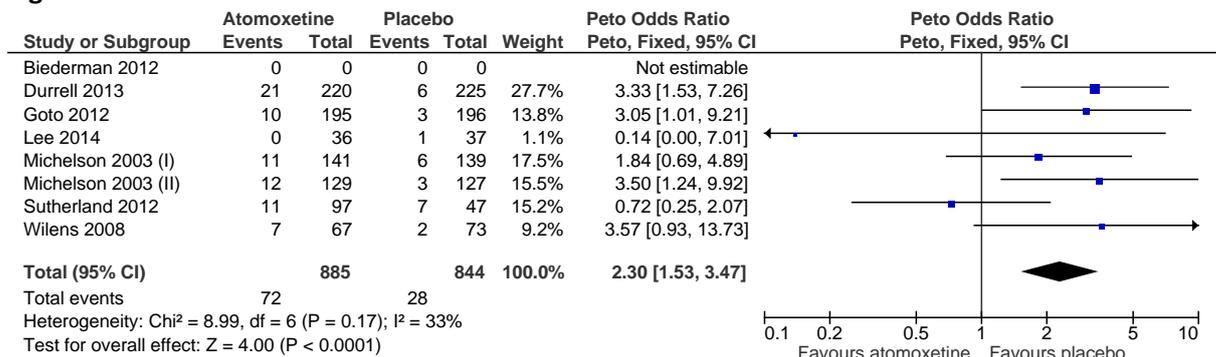
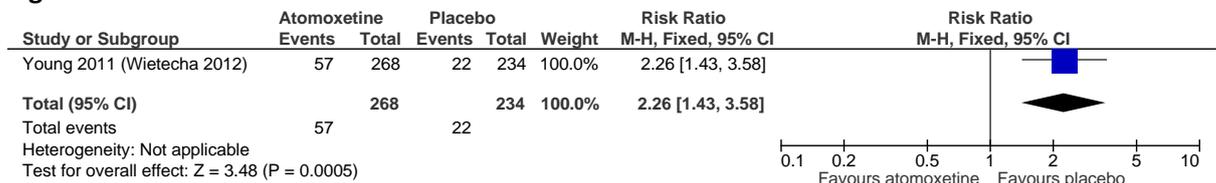


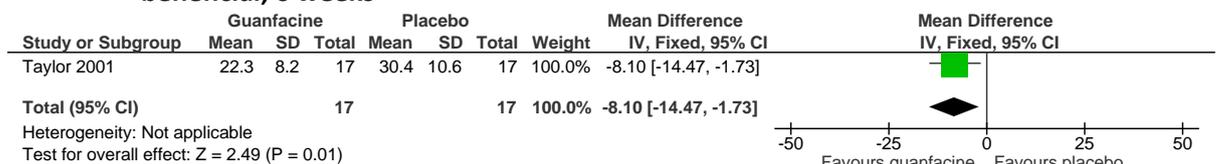
Figure 226: Discontinuation due to adverse events at 24 weeks



2

Guanfacine versus placebo

Figure 227: ADHD total symptoms investigator rated (DSM-IV RS total scores); 0-54; low values are beneficial; 6 weeks



3

Figure 228: ADHD inattention symptoms investigator rated (DSM-IV RS inattentive subscale); 0-27; low values are beneficial; 6 weeks

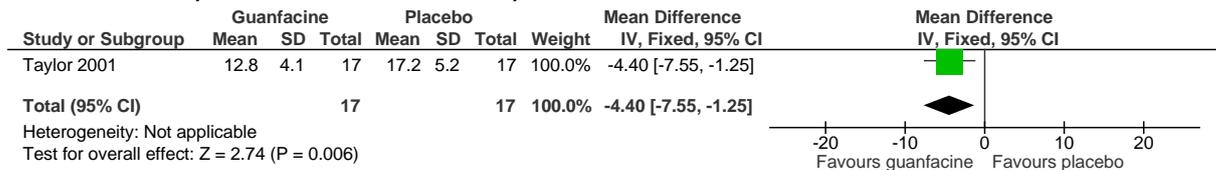
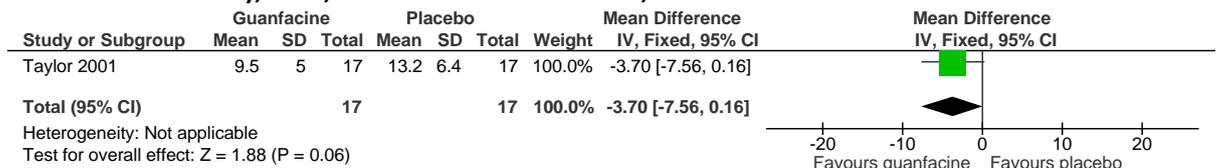
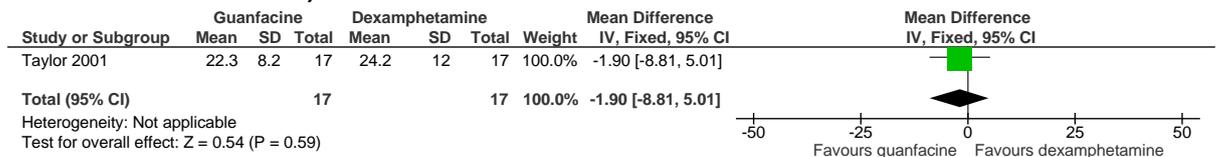


Figure 229: ADHD hyperactivity symptoms investigator rated (DSM-IV RS hyperactive subscale); 0-27; low values are beneficial; 6 weeks



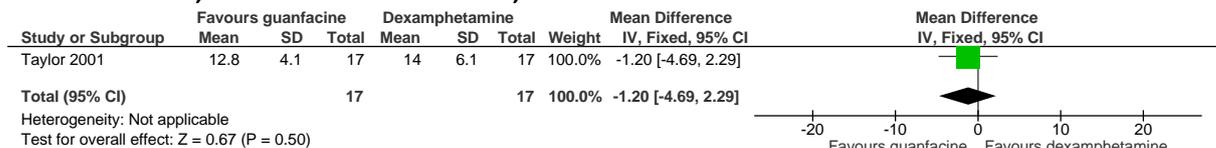
1 **Guanfacine versus dexamphetamine**

Figure 230: ADHD total symptoms investigator rated (DSM-IV RS total scores); 0-54; low values are beneficial; 6 weeks



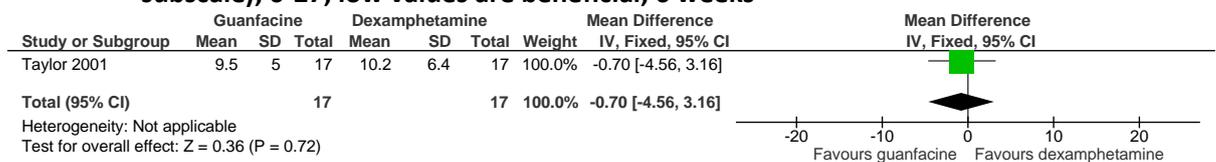
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Figure 231: ADHD inattention symptoms investigator rated (DSM-IV RS inattentive subscale); 0-27; low values are beneficial; 6 weeks



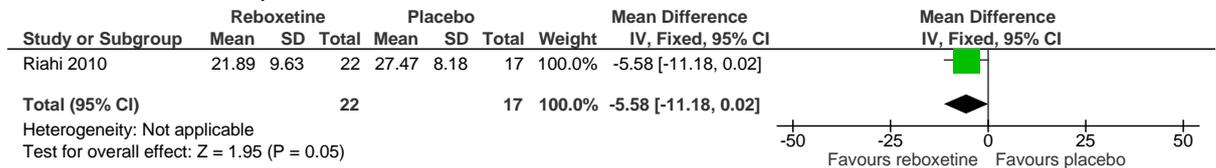
3

Figure 232: ADHD hyperactivity symptoms investigator rated (DSM-IV RS hyperactive subscale); 0-27; low values are beneficial; 6 weeks



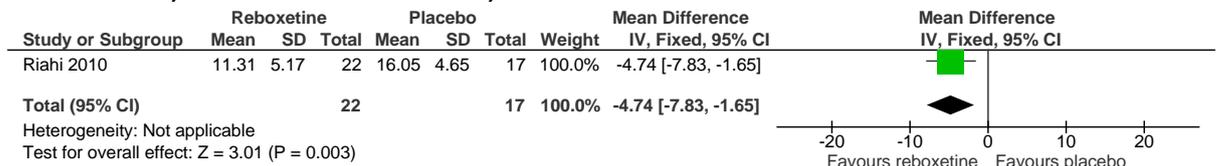
1 **Reboxetine versus placebo**

Figure 233: ADHD total symptoms investigator rated (CAARS total scores); 0-54; low values are beneficial; 6 weeks



2

Figure 234: ADHD inattention symptoms investigator rated (CAARS inattentive subscale) ; 0-27; low values are beneficial; 6 weeks



3

Figure 235: ADHD hyperactivity symptoms investigator rated (CAARS hyperactive subscale); 0-27; low values are beneficial; 6 weeks

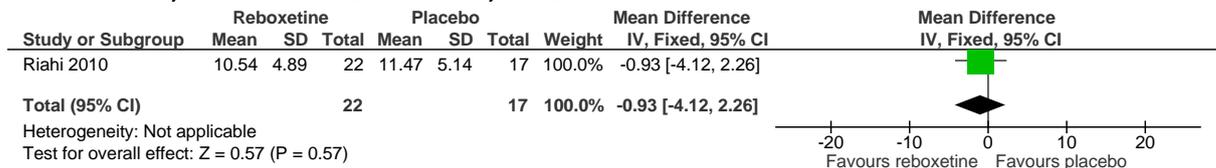
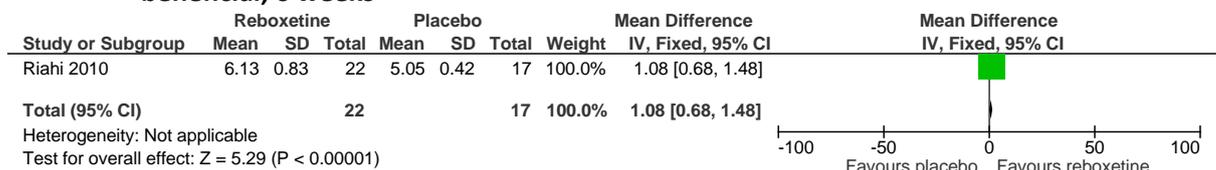
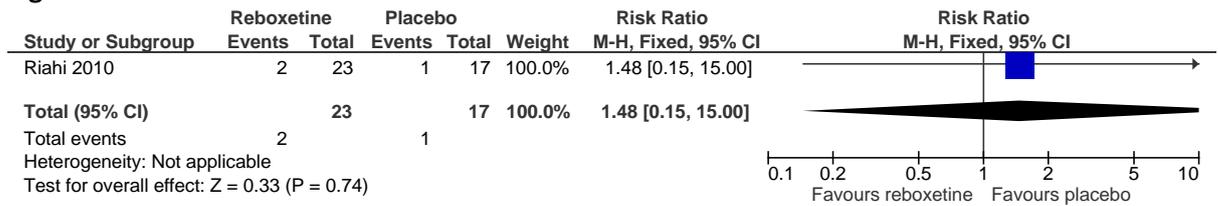


Figure 236: Behavioural outcomes (Global assessment of functioning); 0-100; high values are beneficial; 6 weeks



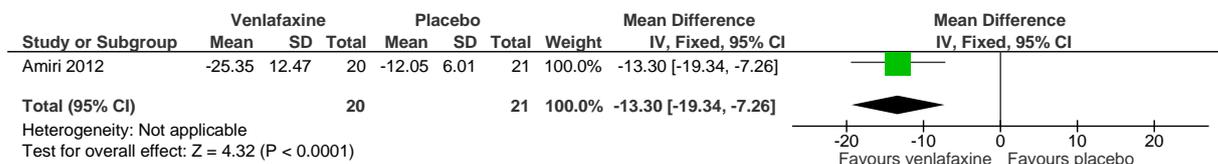
4

Figure 237: Discontinuation due to adverse events at 6 weeks



1 **Venlafaxine versus placebo**

2 **Figure 238: ADHD total symptoms self rated at 6 weeks (CAARS ADHD index); 0-27; low values**
3 **are beneficial**



4
5

Figure 239: ADHD inattention symptoms self rated (CAARS inattentive subscale); 0-27; low values
are beneficial; 6 weeks

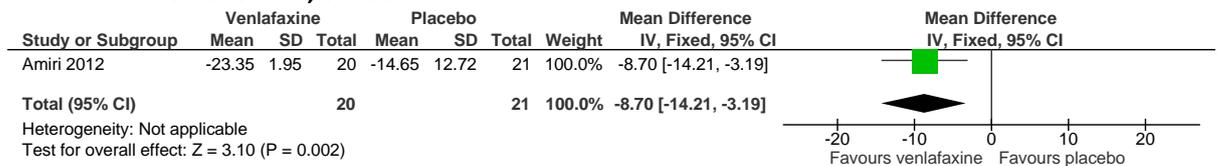
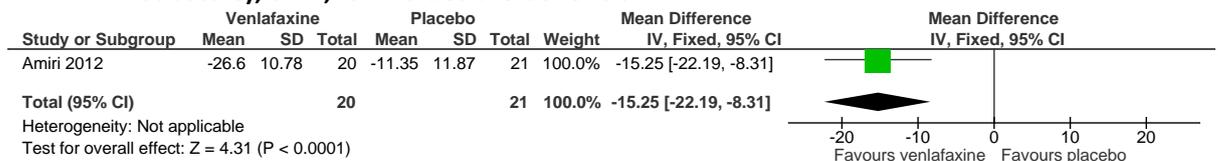
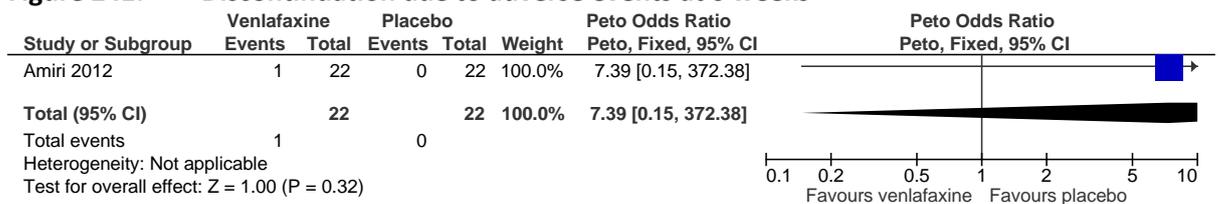


Figure 240: ADHD hyperactivity symptoms self rated at 6 weeks (CAARS hyperactive/impulsive
subscale); 0-27; low values are beneficial



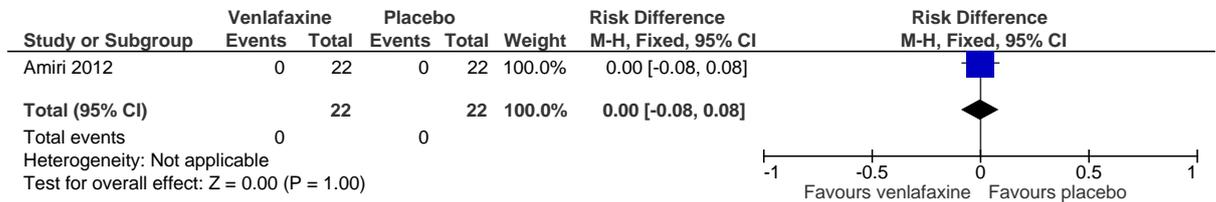
6

Figure 241: Discontinuation due to adverse events at 6 weeks



1

Figure 242: Serious adverse events at 6 weeks

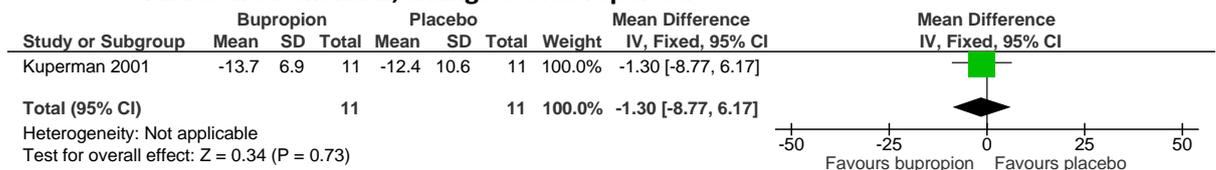


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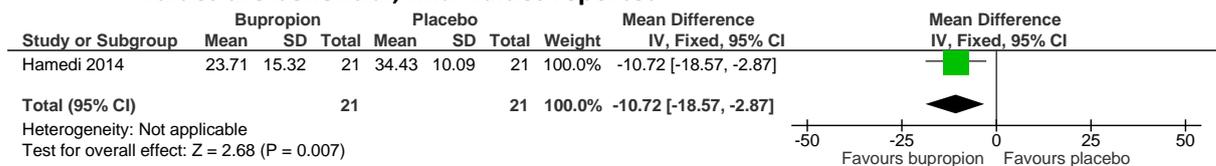
Bupropion versus placebo

Figure 243: ADHD total symptoms investigator rated at 7 weeks (ADHD-RS total score); 0-54; low values are beneficial; change scores reported



4

Figure 244: ADHD total symptoms investigator rated at 6 weeks (CAARStotal score); 0-54; low values are beneficial; final values reported



5

Figure 245: CGI-I score of 1 or 2 at 7 weeks

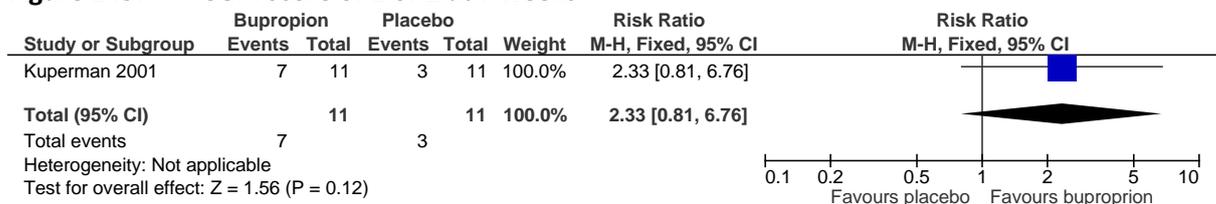
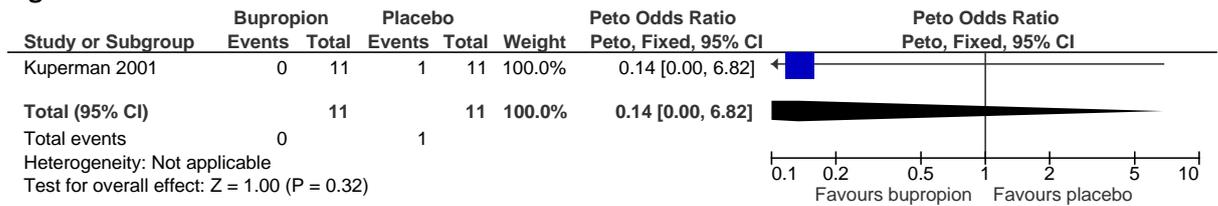


Figure 246: Discontinuation due to adverse events at 7 weeks

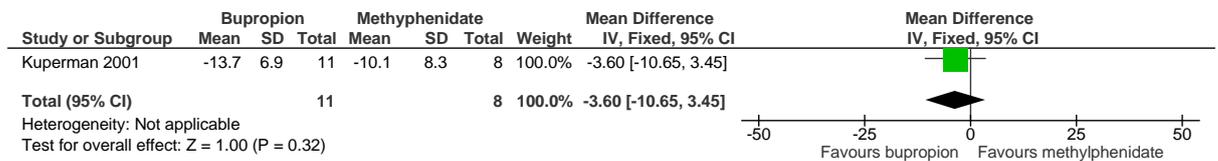


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Bupropion versus methylphenidate

Figure 247: ADHD total symptoms investigator rated at 7 weeks (ADHD-RS total score); 0-54, low values are beneficial



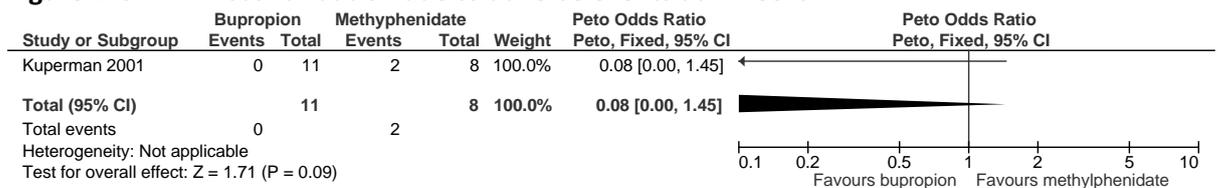
3

Figure 248: CGI-I score of 1 or 2 at 7 weeks



4

Figure 249: Discontinuation due to adverse events at 7 weeks



5

Modafinil versus placebo

Figure 250: Quality of life at 9 weeks (Quality of life enjoyment and satisfaction questionnaire); 0-10, higher values are beneficial

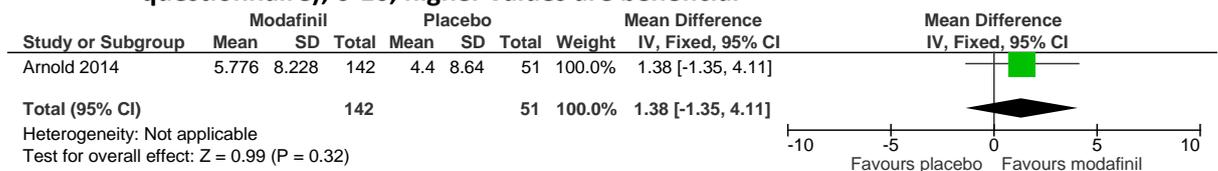


Figure 251: ADHD total symptoms self rated at 9 weeks (Adult ADHD Self report scores; 0-54, lower values are beneficial)

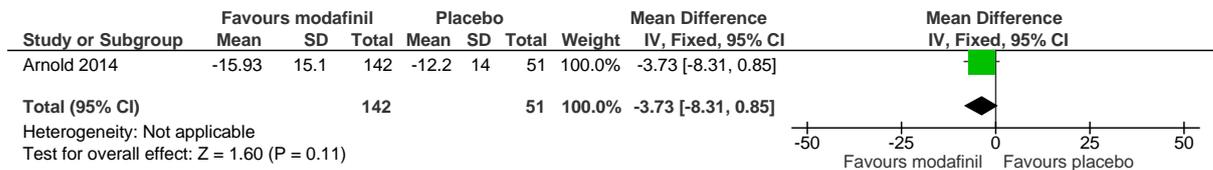


Figure 252: ADHD total symptoms investigator rated at 2 weeks (DSM-IV RS total scores); 0-54, lower values are beneficial)

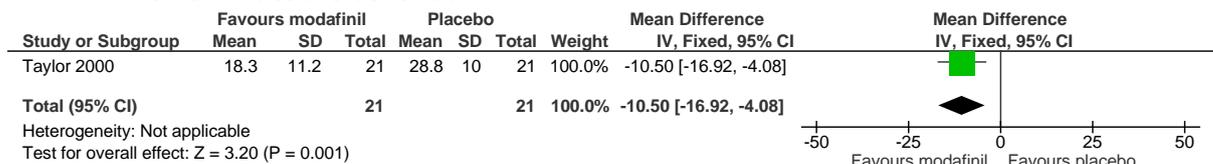


Figure 253: ADHD inattention symptoms investigator rated at 2 weeks (DSM-IV RS Inattentive subscale); 0-27 lower values are beneficial, final values reported

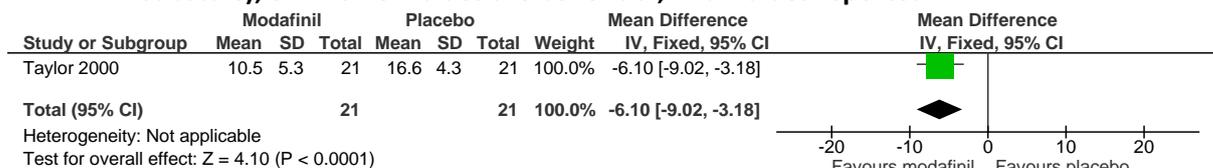


Figure 254: ADHD hyperactivity symptoms investigator rated at 2 weeks (DSM-IV RS Hyperactive subscale); 0-27, lower values are beneficial)

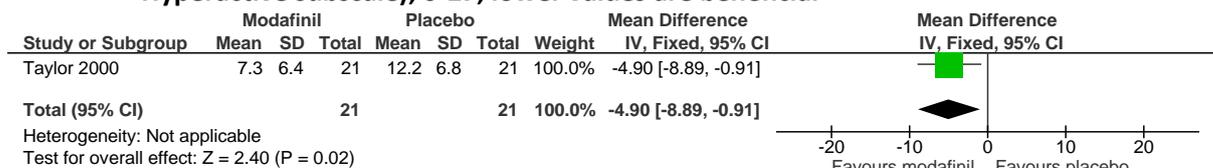


Figure 255: Behavioural outcomes at 9 weeks (BRIEF-A); 0-100, lower values are beneficial)

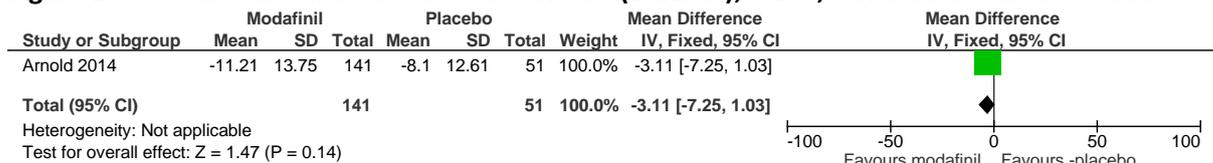
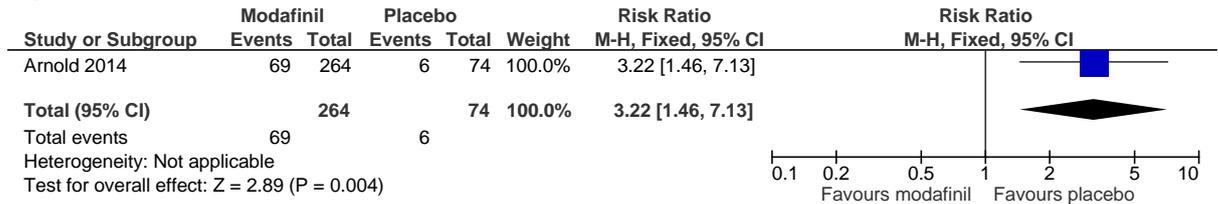
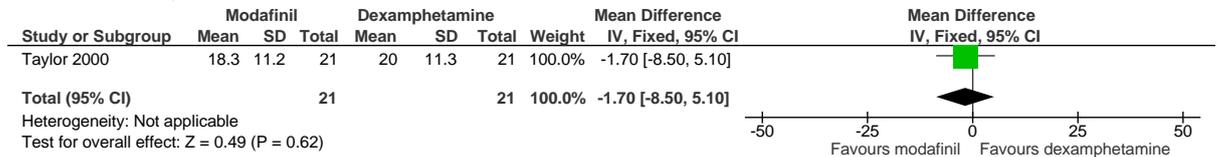


Figure 256: Discontinuation due to adverse events at 7 weeks



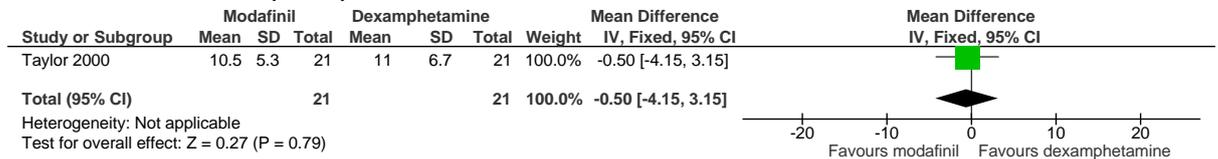
1 **Modafinil versus dexamphetamine**

Figure 257: ADHD total symptoms investigator rated (DSM-IV RS total scores) at 2 weeks; 0-54; lower values are beneficial



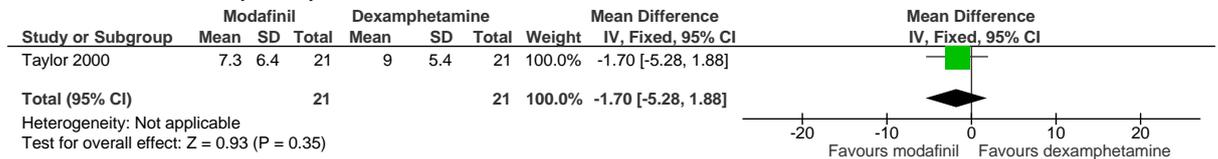
2

Figure 258: ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale) at 2 weeks; 0-27, lower values are beneficial



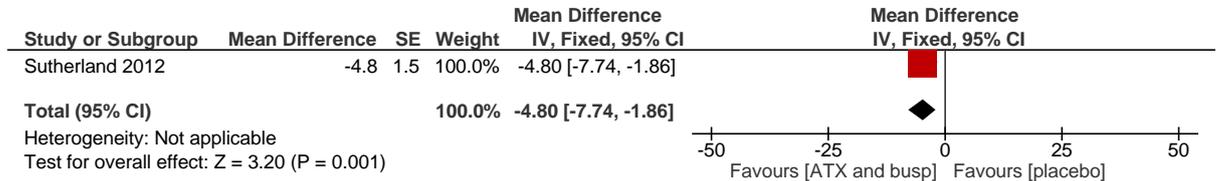
3

Figure 259: ADHD hyperactivity symptoms investigator rated (DSM-IV Hyperactive subscale) at 2 weeks; 0-27, lower values are beneficial



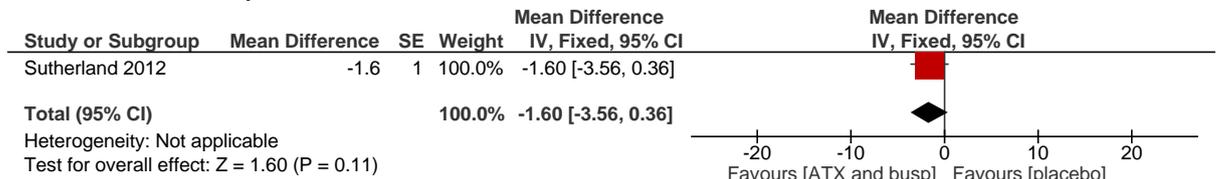
1 **Atomoxetine and bupirone versus placebo**

Figure 260: ADHD total symptoms investigator rated at 8 weeks (AISRS total scores); 0-54; lower values are beneficial



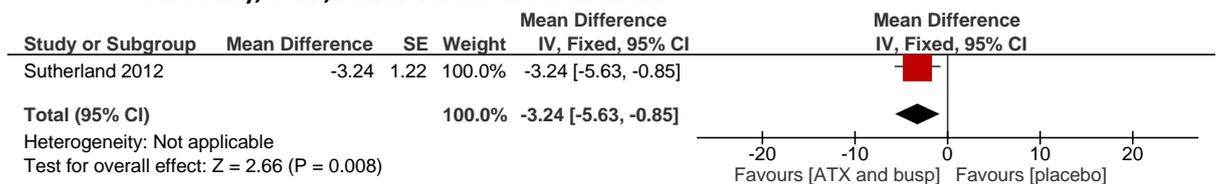
2

Figure 261: ADHD inattention symptoms investigator rated at 8 weeks (AISRS inattention subscale); 0-27; lower values are beneficial



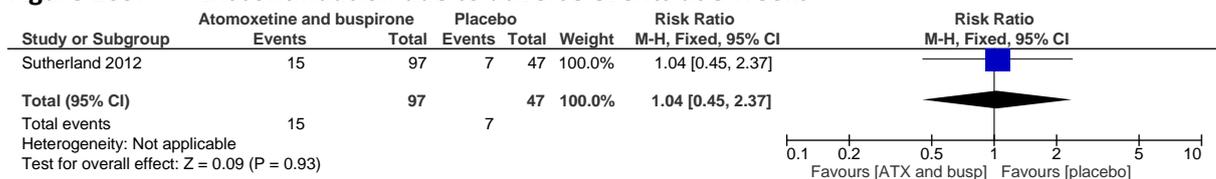
3

Figure 262: ADHD hyperactivity symptoms investigator rated at 8 weeks (AISRS hyperactivity subscale); 0-27; lower values are beneficial



4

Figure 263: Discontinuation due to adverse events at 8 weeks



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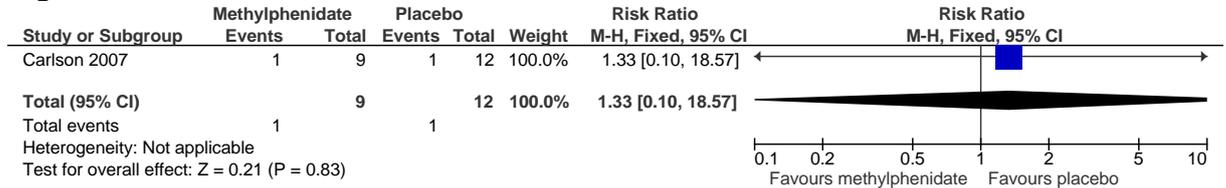
6

7

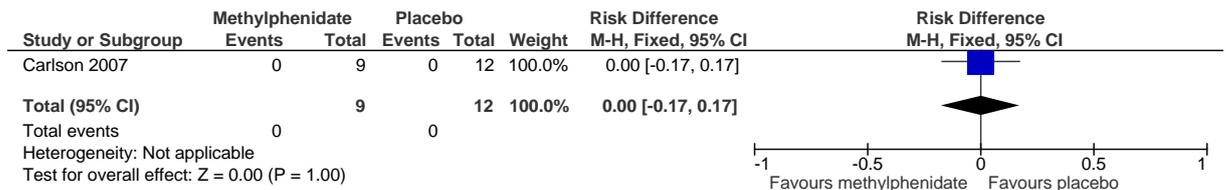
1 **E.2 Pharmacological sequencing**

2 **E.2.1 Methylphenidate versus placebo in children with ADHD not responding to**
3 **atomoxetine**

4 **Figure 264: Discontinued treatment due to adverse events**



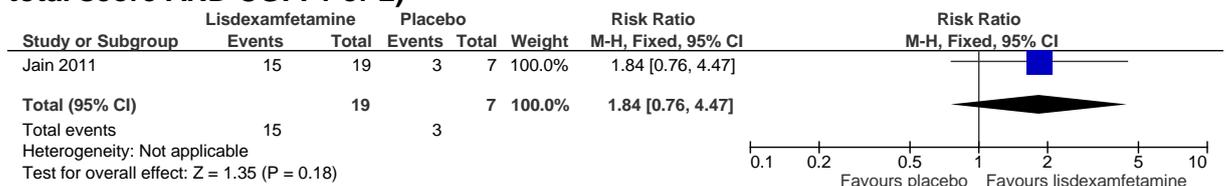
6 **Figure 265: Adverse events leading to hospitalisation/death/disability**



7

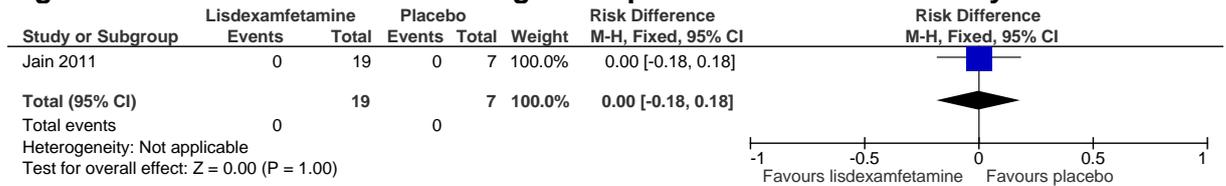
8 **E.2.2 Lisdexamfetamine dimesylate versus placebo in children with ADHD who had**
9 **not responded to previous methylphenidate treatment**

10 **Figure 266: ADHD symptoms (Clinical response: $\geq 30\%$ reduction in ADHD-RS-IV**
11 **total score AND CGI-I 1 or 2)**



12

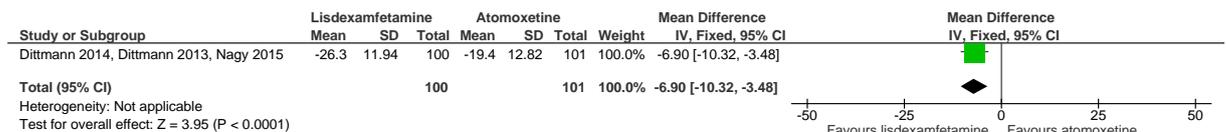
13 **Figure 267: Adverse events leading to hospitalisation/death/disability**



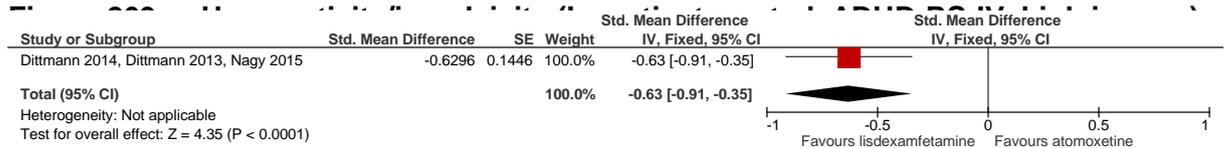
14

15 **E.2.3 Lisdexamfetamine dimesylate versus atomoxetine in children with ADHD who**
16 **had an inadequate response to previous methylphenidate treatment**

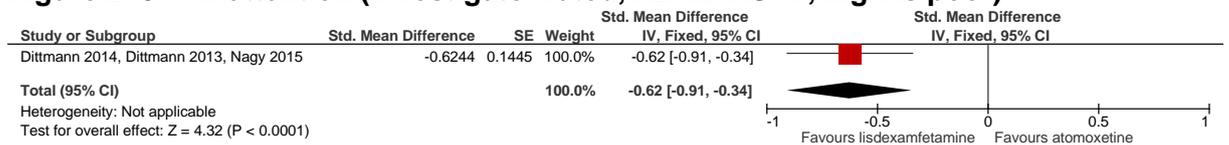
17 **Figure 268: ADHD total symptoms (investigator rated ADHD-RS-IV, change score, 0-**
18 **54, high is poor)**



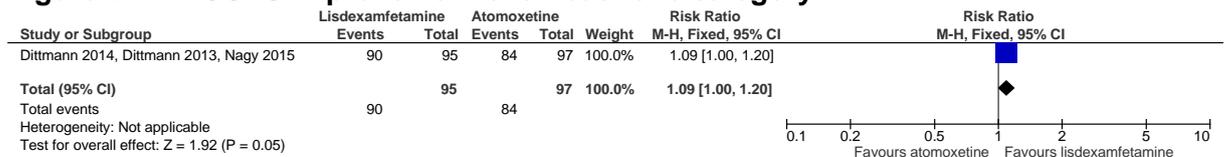
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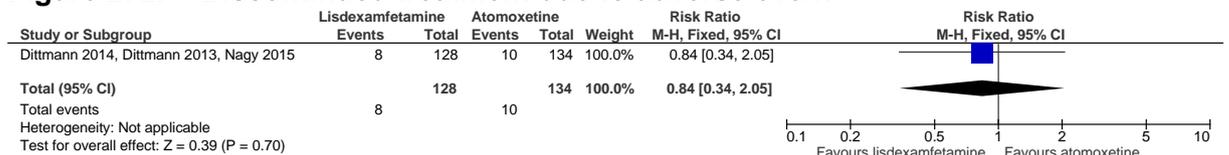
2
3 **Figure 270: Inattention (Investigator rated, ADHD-RS-IV, high is poor)**



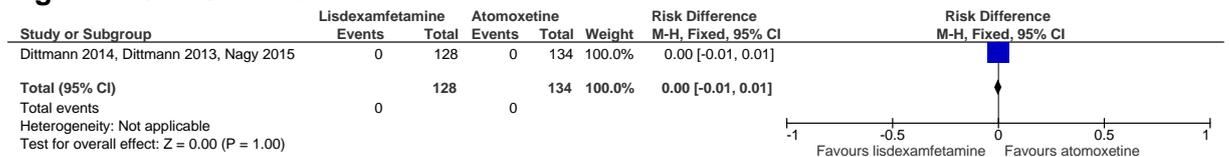
5 **Figure 271: CGI-S improvement of at least one category**



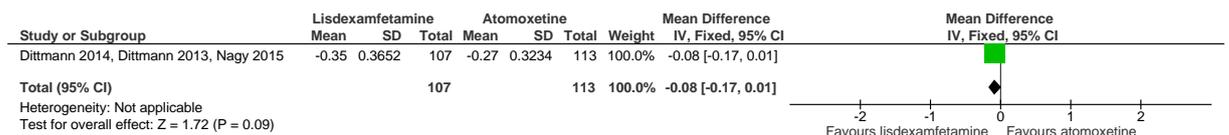
7 **Figure 272: Discontinued treatment due to adverse event**



9 **Figure 273: Serious TEAE**



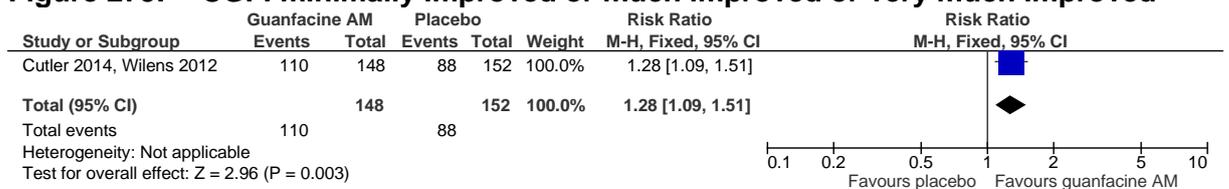
11 **Figure 274: Function/behaviour (Parent rated, WFIRS-P, 0-3, high is poor)**



13 **Adults**

14 **E.2.4 Guanfacine AM versus placebo in children with ADHD are taking CNS**
15 **stimulants but have a partial or suboptimal response**

16 **Figure 275: CGI-I minimally improved or much improved or very much improved**



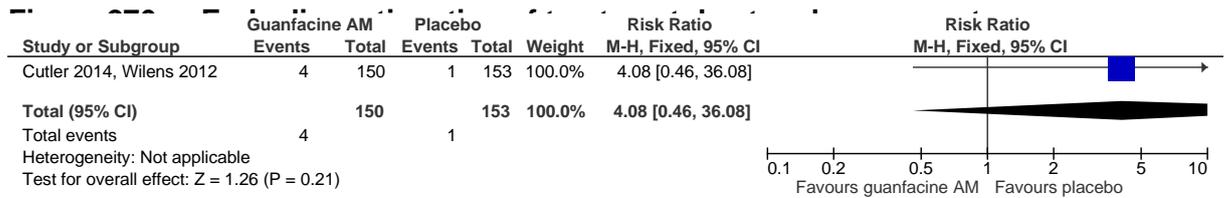


Figure 277: Adverse events leading to hospitalisation/death/disability (severe TEAEs)

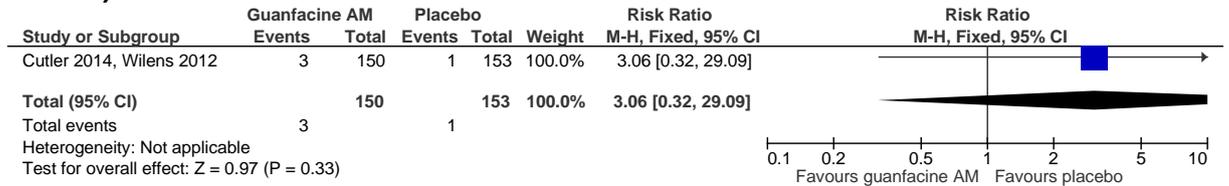


Figure 278: ADHD symptoms (ADHD-RS-IV inattention subscale)

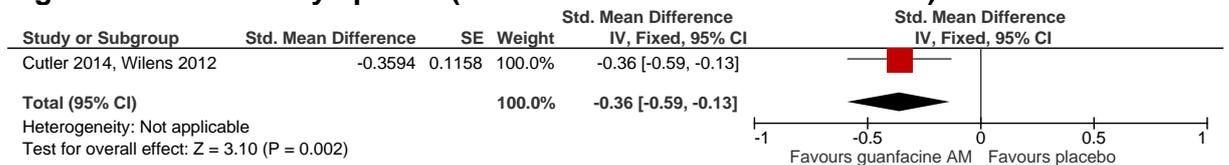


Figure 279: ADHD symptoms (ADHD-RS-IV)

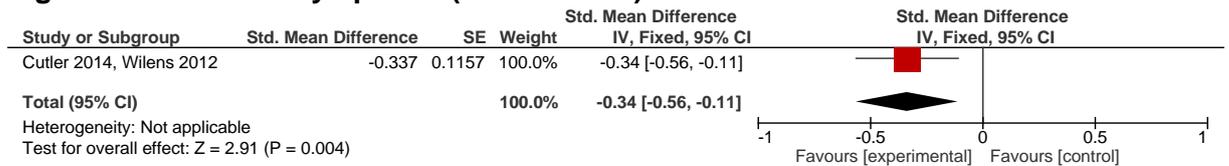
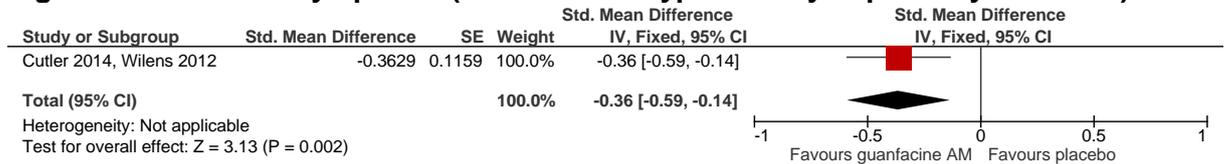


Figure 280: ADHD symptoms (ADHD-RS-IV hyperactivity/impulsivity subscale)



E.2.5 Guanfacine PM versus placebo in children with ADHD are taking CNS stimulants but have a partial or suboptimal response

Figure 281: CGI-I minimally improved or much improved or very much improved

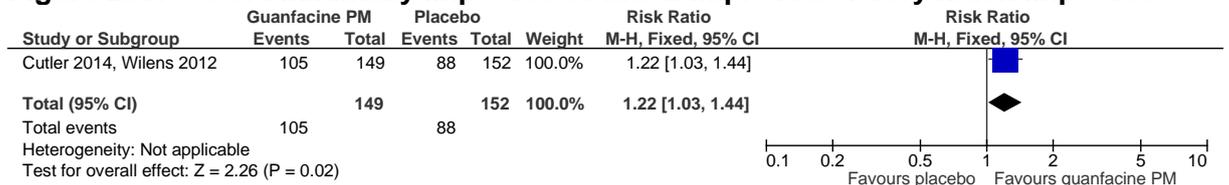


Figure 282: Early discontinuation of treatment due to adverse events

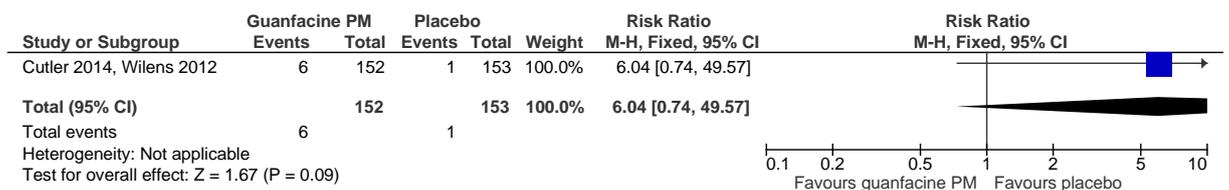


Figure 283: Adverse events leading to hospitalisation/death/disability (severe)

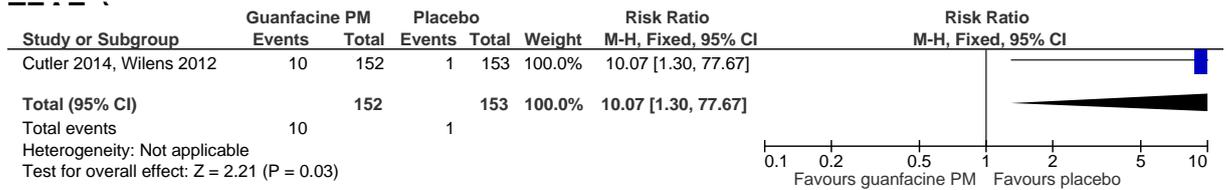


Figure 284: ADHD symptoms (ADHD-RS-IV inattention subscale)

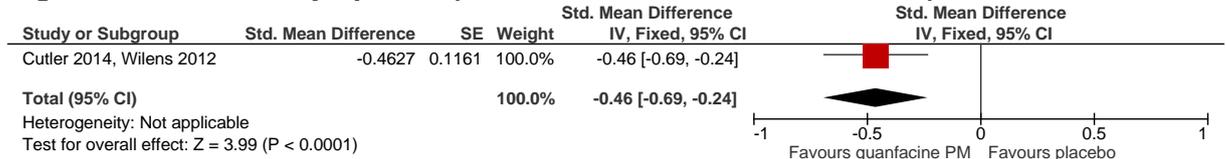


Figure 285: ADHD symptoms (ADHD-RS-IV)

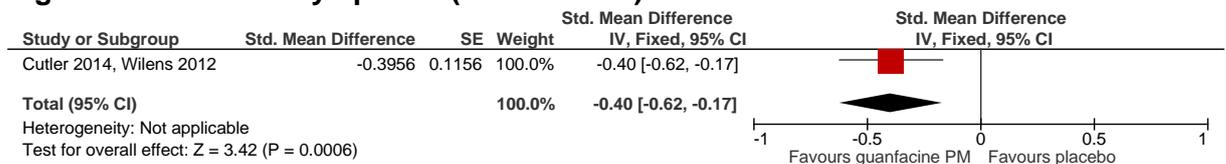
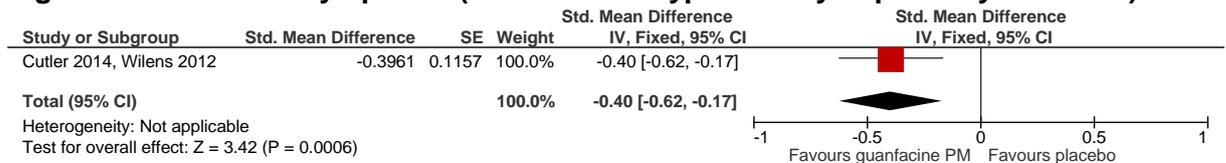


Figure 286: ADHD symptoms (ADHD-RS-IV hyperactivity/impulsivity subscale)



E.2.6 Clonidine versus placebo in children with ADHD and insufficient response to stimulant treatment

Figure 287: ADHD total symptoms (ADHD-RS-IV improvement, high is poor)

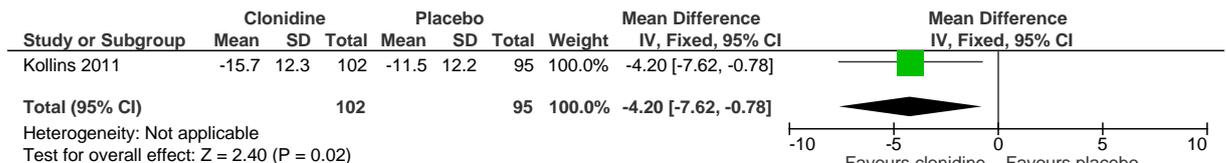


Figure 288: Inattention (ADHD-RS-IV, high is poor)

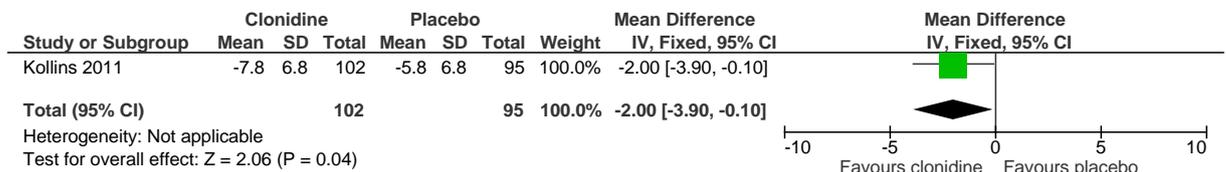
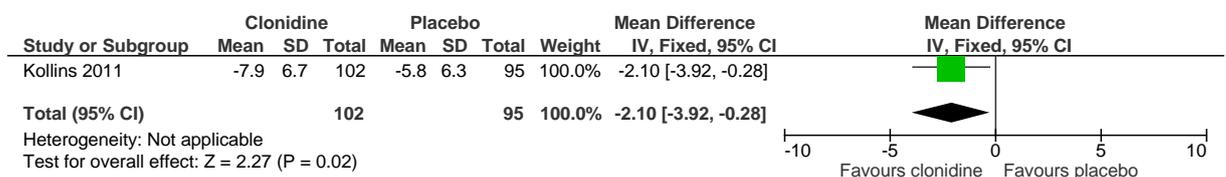
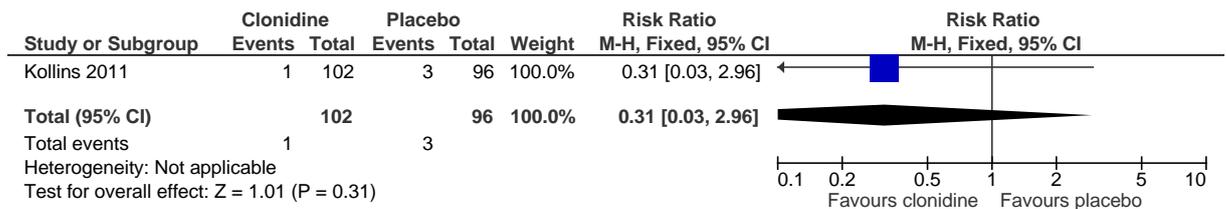


Figure 289: Hyperactivity/impulsivity (ADHD-RS-IV, high is poor)

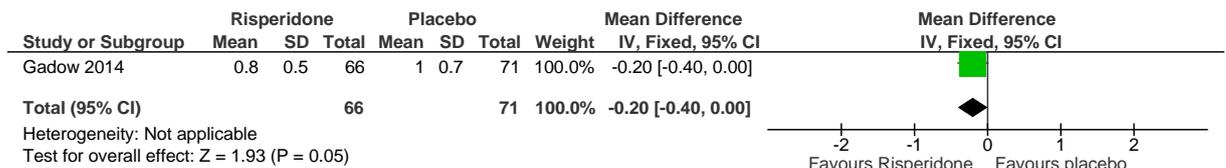


1 **Figure 290: Discontinued treatment due to TEAE**

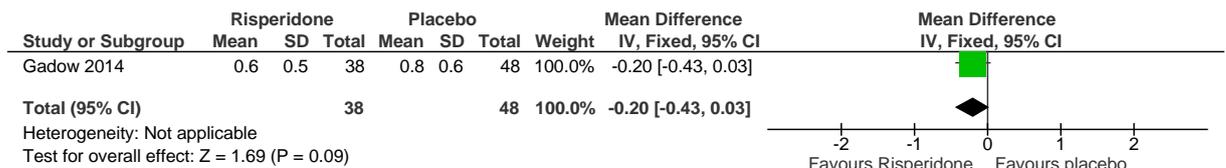


2
3 **E.2.7 Risperidone versus placebo in children with ADHD who do not show sufficient**
4 **clinical response to methylphenidate**

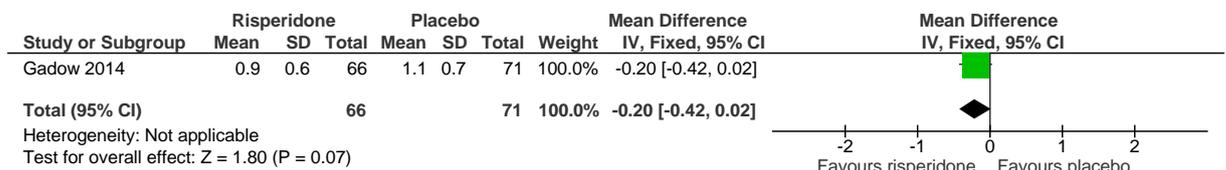
5 **Figure 291: ADHD total symptoms (parent rated ADHD-SC4, Severity Score, 0-3, high**
6 **is poor)**



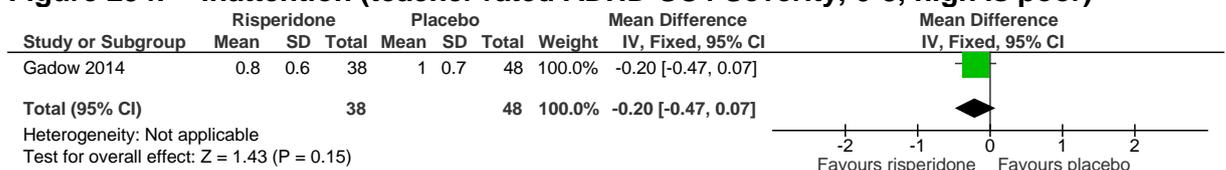
7
8 **Figure 292: ADHD total symptoms (teacher rated ADHD-SC4, Severity Score, 0-3,**
9 **high is poor)**



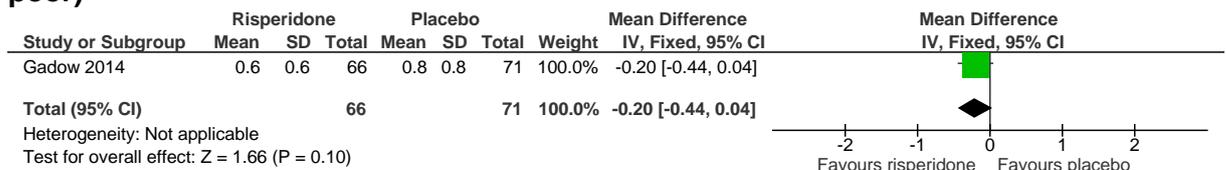
10
11 **Figure 293: Inattention (parent rated ADHD-SC4 Severity, 0-3, high is poor)**



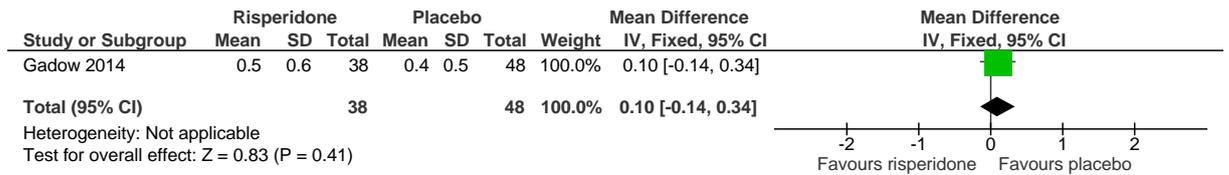
12
13 **Figure 294: Inattention (teacher rated ADHD-SC4 Severity, 0-3, high is poor)**



14
15 **Figure 295: Hyperactivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is**
16 **poor)**



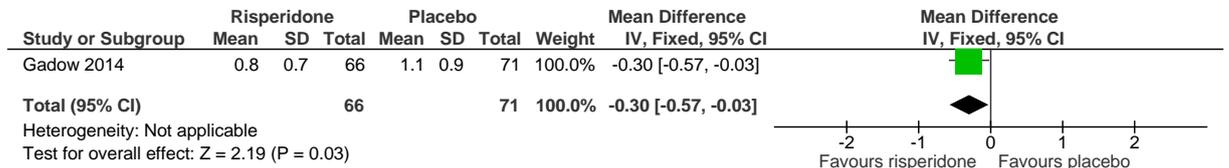
17
18 **Figure 296: Hyperactivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is**
19 **poor)**



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Figure 297: Impulsivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor)

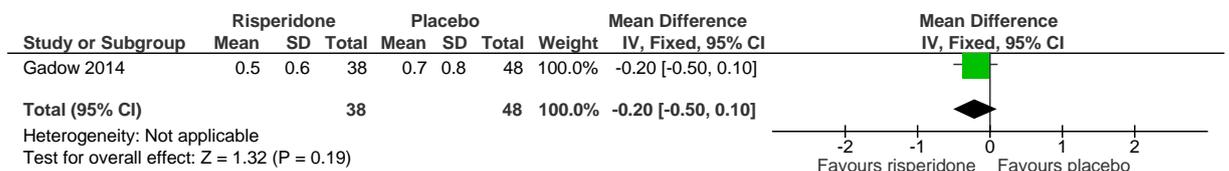


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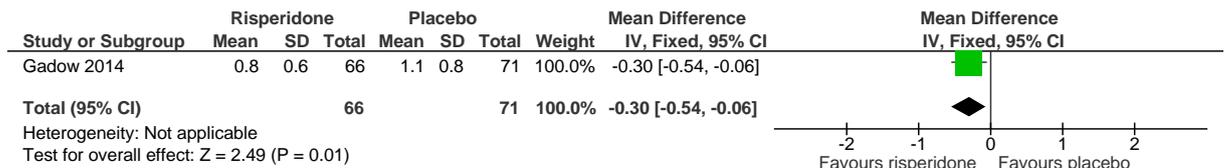
Figure 298: Impulsivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor)



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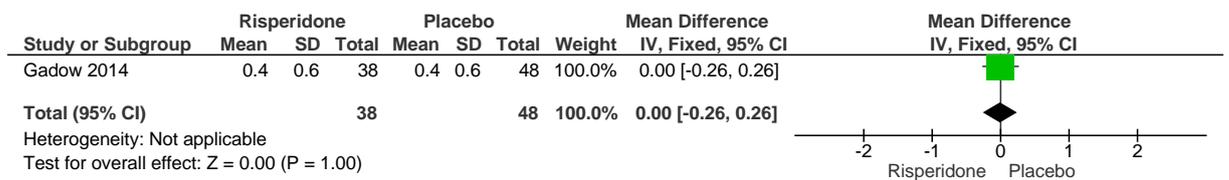
Figure 299: Function/behaviour (parent rated ODD DSM-IV, 0-3, high is poor)



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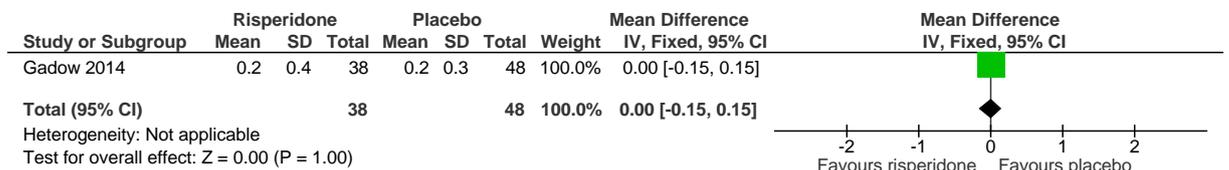
Figure 300: Function/behaviour (teacher rated ODD DSM-IV, 0-3, high is poor)



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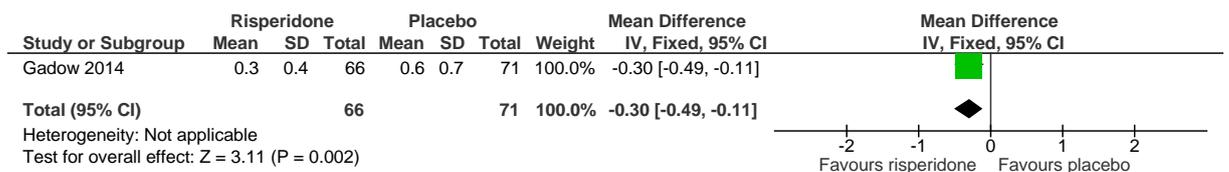
Figure 301: Function/behaviour (teacher rated Peer Conflict Scale, 0-3, high is poor)



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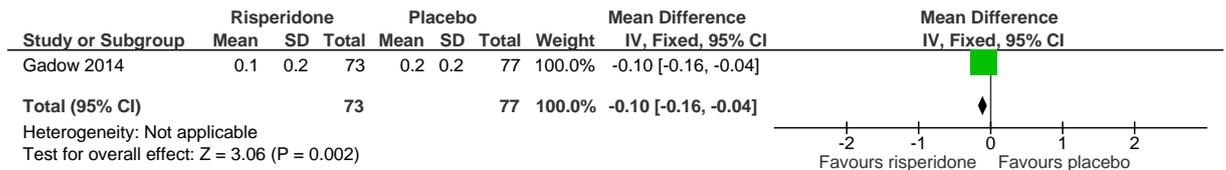
Figure 302: Function/behaviour (parent rated Peer Conflict Scale, 0-3, high is poor)



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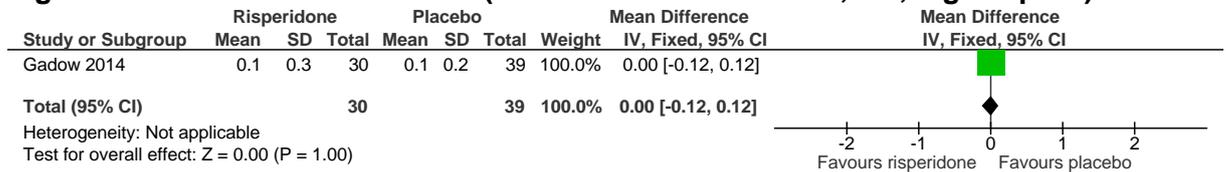
Figure 303: Function/behaviour (parent rated CD DSM-IV, 0-3, high is poor)



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Figure 304: Function/behaviour (teacher rated CD DSM-IV, 0-3, high is poor)



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E.2.8 Guanfacine versus placebo in adults with a sub-optimal response to CNS stimulants

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Figure 305: ADHD total symptoms (ADHD-RS, 0-54, high is poor)

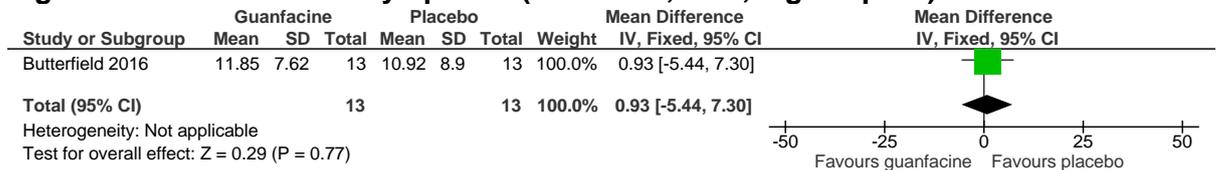


Figure 306: CGI-S (change score, 0-7, high scores are beneficial)

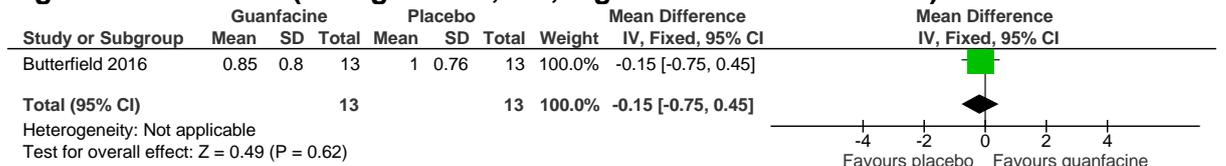
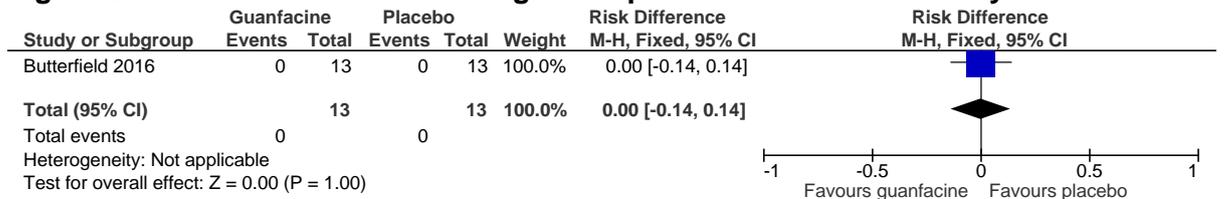


Figure 307: Adverse events leading to hospitalisation/death/disability



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Appendix F: GRADE tables

F.1 Pharmacological efficacy

F.1.1 Pre-school children (under the age of 5)

Table 78: Clinical evidence profile: methylphenidate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate versus placebo (pre-school - to add to R/V)	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (SNAP-IV total scores, parent-teacher rated); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	13/53 (24.5%)	7/61 (11.5%)	RR 2.14 (0.92 to 4.96)	131 more per 1000 (from 9 fewer to 454 more)	LOW	CRITICAL
ADHD total symptoms parent rated (CPRS DSM-IV ADHD subscale); 0-54, lower values are beneficial; 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	7	7	-	MD 8.92 lower (17.97 lower to 0.13 higher)	LOW	CRITICAL
Behavioural symptoms (WFIRS-P scale) (Better indicated by lower values); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	7	7	-	MD 4.83 lower (11.13 lower to 1.47 higher)	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 79: Clinical evidence profile: Risperidone versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD-RS Total score (follow-up 6 weeks; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	18	15	-	MD 1.34 higher (4.21 lower to 6.89 higher)	VERY LOW	CRITICAL
ADHD-RS Inattentive subscale (follow-up 6 weeks; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	18	15	-	MD 0.74 higher (2.04 lower to 3.52 higher)	VERY LOW	IMPORTANT
ADHD-RS Hyperactive subscale (follow-up mean 6 weeks; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	18	15	-	MD 0.31 higher (3.18 lower to 3.80 higher)	VERY LOW	IMPORTANT
Discontinuation due to side effects (follow-up 6 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	2/20 (10%)	3/18 (16.7%)	RR 0.6 (0.11 to 3.19)	67 fewer per 1000 (from 148 fewer to 365 more)	VERY 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 confidence interval crossed both MIDs.

Table 80: Clinical evidence profile: Methylphenidate and risperidone versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone	Standard Treatment	Relative (95% CI)	Absolute		
ADHD Symptoms Total (6 weeks PT; parent rated; CPRS, high is poor)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	21	21	-	MD 3.33 lower (12.72 lower to 6.06 higher)	VERY LOW	CRITICAL
ADHD Inattention (6 weeks PT; parent rated; CPRS; high is poor)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	21	21	-	MD 0.00 higher (2.35 lower to 2.35 higher)	VERY LOW	CRITICAL
ADHD Hyperactivity symptoms (6 weeks PT; parent rated; CPRS; high is poor)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	21	21	-	MD 0.38 higher (1.95 lower to 2.71 higher)	VERY LOW	CRITICAL
CGI-I (6 weeks PT)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	16/21 (76.2%)	13/21 (61.9%)	RR 1.23 (0.82 to 1.86)	142 more per 1000 (from 111 fewer to 532 more)	VERY LOW	CRITICAL
Behaviour outcomes (6 weeks PT; parent rated; CPRS; high is poor)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	21	21	-	MD 1.52 lower (3.82 lower to 0.78 higher)	VERY LOW	IMPORTANT
Discontinued due to adverse events (6 weeks PT)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious indirectness	none	5/21 (23.8%)	0/21 (0%)	RR 11.00 (0.65 to 187.17)	-	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.

⁴ Downgrade by 2 increments if the confidence interval crossed both MIDs.

4 F.1.2 Children and young people (aged 5 to 18)

5 **Table 81: Clinical evidence profile: IR methylphenidate versus placebo**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate release methylphenidate versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms parent rated (Abbreviated parent rating scale and Conners ADHD index; lower values are beneficial); 4-7 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	31	-	SMD 0.53 lower (0.91 to 0.16 lower)	MODERATE	CRITICAL
ADHD total symptoms parent rated (ASQ-P; 0-20; low values are beneficial; change scores reported); 16 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	65	63	-	MD 3.71 lower (6.71 to 0.7 lower)	LOW	CRITICAL
ADHD total symptoms parent rated, (Conners ADHD index; PT; 0-30; low values are beneficial; final values reported); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	61	-	MD 3.3 lower (3.75 to 2.85 lower)	MODERATE	CRITICAL
ADHD total symptoms teacher rated (Conners ADHD index and abbreviated parent rating scale; lower values are beneficial; final values reported; crossover trials); 4-7 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	31	-	SMD 0.94 lower (1.33 to 0.55 lower)	MODERATE	CRITICAL
ADHD total symptoms teacher rated (ASQ-T; 0-20; low values are beneficial; change scores reported); 16 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	65	63	-	MD 2.93 lower (5.51 to 0.36 lower)	LOW	CRITICAL
ADHD total symptoms teacher rated, (Conners ADHD index; 0-30; lower values are beneficial; final values reported); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	61	-	MD 4.1 lower (4.54 to 3.66 lower)	MODERATE	CRITICAL

ADHD hyperactivity symptoms parent rated; (SNAP-IV and parent symptom questionnaire; 4-8 weeks)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	113	108	-	SMD 0.92 lower (1.2 to 0.64 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms parent rated; (Conners Parent ADHD Index Hyperactivity subscale), 0-15, lower values are beneficial; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	61	61	-	MD 1.5 lower (3.44 lower to 0.44 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale; 0-3, PT; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	94	89	-	MD 0.31 lower (0.55 to 0.07 lower)	LOW	CRITICAL
ADHD hyperactivity symptoms teacher rated (Conners Teacher ADHD Index (Hyperactivity); 0-15, lower values are beneficial); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	61	61	-	MD 2.6 lower (4.68 to 0.52 lower)	LOW	CRITICAL
ADHD inattention symptoms teacher rated; (SNAP-IV inattention subscale; 0-3; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	89	-	MD 0.71 lower (0.94 to 0.48 lower)	MODERATE	CRITICAL
ADHD inattention symptoms parent rated; (SNAP-IV inattention subscale; 0-3; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	89	-	MD 0.61 lower (0.83 to 0.39 lower)	MODERATE	CRITICAL
CGI score of 1 or 2; 3-9 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	183/269 (68%)	98/263 (37.3%)	RR 1.85 (1.56 to 2.19)	317 more per 1000 (from 209 more to 443 more)	MODERATE	CRITICAL
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial; 16 weeks												

2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	64	62	-	MD 9.15 higher (4.21 to 14.08 higher)	LOW	IMPORTANT
Discontinued due to adverse events at 3 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	3/175 (1.7%)	0/177 (0%)	OR 7.3 (0.76 to 70.45)	-	LOW	CRITICAL
Discontinued due to adverse events at 16 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	6/90 (6.7%)	0/91 (0%)	OR 7.87 (1.55 to 39.86)	-	LOW	CRITICAL
Serious adverse events at 3 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/155 (0%)	0/159 (0%)	See comment	-	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 82: Clinical evidence profile: OROS methylphenidate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OROS Methylphenidate versus placebo	Control	Relative (95% CI)	Absolute		
Quality of life (Child Health Questionnaire); 0-100, higher values are beneficial); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	75	27	-	MD 8.4 higher (3.14 to 13.66 higher)	LOW	CRITICAL
ADHD total symptoms parent rated (Conners Parent Rating Scale; 0-54, lower values are beneficial, change scores); 8 weeks												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none ¹	82	27	-	MD 9.6 lower (13.67 to 5.53 lower)	MODERATE	CRITICAL
ADHD total symptoms parent rated (SNAP-IV, 0-3, lower values are beneficial; final values); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 0.41 lower (0.79 to 0.03 lower)	MODERATE	CRITICAL
ADHD total symptoms teacher rated (SNAP-IV; 0-3, lower values are beneficial); 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	19	19	-	MD 0.37 lower (0.69 to 0.05 lower)	MODERATE	CRITICAL
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial; 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	42	-	MD 13 lower (16.05 to 9.95 lower)	MODERATE	CRITICAL
ADHD inattention symptoms investigator rated (ADHD-RS Inattentive subscale); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	82	27	-	MD 5.8 lower (9 to 2.6 lower)	VERY LOW	CRITICAL
ADHD inattention symptoms teacher rated (SNAP-IV Inattentive subscale); 0-3 Lower values are beneficial; 4 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	113	108	-	MD 0.54 lower (0.74 to 0.34 lower)	LOW	CRITICAL
ADHD inattention symptoms parent rated (SNAP-IV Inattentive subscale); 0-3, lower values are beneficial, change scores reported; 4 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	113	108	-	MD 0.57 lower (0.75 to 0.38 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms investigator rated (ADHD-RS Hyperactive subscale); 0-27, Lower values are beneficial, change scores reported; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	82	27	-	MD 4.9 lower (7.47 to 2.33 lower)	VERY LOW	CRITICAL
ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale); 0-3 Lower values are beneficial, change scores reported; 4 weeks												
2	randomised trials	serious ¹	no serious	no serious	no serious	none	113	108	-	MD 0.67 lower	MODERATE	CRITICAL

	trials		inconsistency	indirectness	imprecision					(0.87 to 0.47 lower)		
ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale); 0-3 Lower values are beneficial, change scores reported; 4 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	113	108	-	MD 0.63 lower (0.83 to 0.43 lower)	MODERATE	CRITICAL
Clinical global impressions – improvement (score of 1 or 2); 4-7 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	101/201 (50.2%)	28/195 (14.4%)	RR 3.5 (2.42 to 5.06)	359 more per 1000 (from 204 more to 583 more)	MODERATE	CRITICAL
Behavioural outcomes (WFIRS-P total; 0-3, lower values are beneficial); 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	111	111	-	SMD 0.77 lower (1.23 to 0.31 lower)	LOW	IMPORTANT
Academic achievement (CHIP-CE academic achievement subscale; 0-100; high scores are beneficial; 7 weeks)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	110	-	MD 8.4 higher (5.59 to 11.21 higher)	LOW	IMPORTANT
Discontinuation due to adverse events; 4-7 weeks												
3	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/297 (1.7%)	6/285 (2.1%)	RR 0.81 (0.25 to 2.62)	4 fewer per 1000 (from 16 fewer to 34 more)	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 Downgrade by 2 increments if the confidence interval crossed both MIDs

Table 83: Clinical evidence profile: IR methylphenidate versus OROS methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	IR Methylphenidate	Control	Relative	Absolute		

studies		bias				considerations	versus OROS Methylphenidate		(95% CI)			
ADHD inattention symptoms teacher rated (SNAP-IV inattention subscale; 0-3; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	97	-	MD 0.08 lower (0.31 lower to 0.15 higher)	MODERATE	CRITICAL
ADHD inattention symptoms parent rated (SNAP-IV inattention subscale; 0-3; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	95	-	MD 0.01 higher (0.19 lower to 0.21 higher)	MODERATE	CRITICAL
ADHD hyperactivity symptoms teacher rated (SNAP-IV hyperactivity subscale; 0-3; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	94	-	MD 0.03 lower (0.26 lower to 0.2 higher)	MODERATE	CRITICAL
ADHD hyperactivity symptoms parent rated (SNAP-IV hyperactivity subscale; 0-3; lower values are beneficial); 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	94	-	MD 0.01 lower (0.2 lower to 0.18 higher)	MODERATE	CRITICAL
CGI-I score of 1 or 2; 4 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	45/95 (47.4%)	44/94 (46.8%)	RR 1.01 (0.75 to 1.37)	10 more per 1000 (from 140 fewer to 150 more)	LOW	CRITICAL
Discontinuation due to adverse events; 4 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	1/94 (1.1%)	1/89 (1.1%)	RR 0.95 (0.06 to 14.91)	1 fewer per 1000 (from 11 fewer to 156 more)	LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs

Table 84: Clinical evidence profile: lisdexamfetamine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lisdexamfetamine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial; change scores reported; 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	113	111	-	MD 18.6 lower (20.98 to 16.22 lower)	MODERATE	CRITICAL
Treatment Response (CGI-I); 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/104 (72.1%)	13/106 (12.3%)	RR 5.88 (3.49 to 9.92)	598 more per 1000 (from 305 more to 1000 more)	MODERATE	CRITICAL
CHIP-CE academic achievement subscale (Better indicated by lower values); 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	110	-	MD 11 higher (8.28 to 13.72 higher)	MODERATE	IMPORTANT
Behaviour outcomes (WFIRS-P) (Better indicated by lower values); 7 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious ²	none	111	110	-	MD 0.33 lower (0.45 to 0.21 lower)	MODERATE	IMPORTANT
Discontinuation due to adverse events; 7 weeks												
2	randomised trials	no serious risk of bias	Serious ³	no serious indirectness	Very serious ²	none	25/331 (7.6%)	5/183 (2.7%)	RR 2.69 (0.93 to 7.74)	46 more per 1000 (from 2 fewer to 184 more)	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..

³Downgraded due to heterogeneity, unexplained by subgroup analysis

Table 85: Clinical evidence profile: methylphenidate versus lisdexamfetamine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate versus lisdexamfetamine	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial; change scores reported; 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	113	111	-	MD 5.6 higher (2.95 to 8.25 higher)	MODERATE	CRITICAL
Treatment Response (CGI-I); 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	Serious ²	57/107 (53.3%)	75/104 (72.1%)	RR 0.74 (0.6 to 0.91)	188 fewer per 1000 (from 65 fewer to 288 fewer)	LOW	CRITICAL
Behaviour outcomes (WFIRS-P) (Better indicated by lower values); 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	111	111	-	SMD 0.08 higher (0.04 lower to 0.20 higher)	LOW	IMPORTANT
CHIP-CE academic achievement subscale (Better indicated by lower values); 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	111	111	-	MD 2.6 lower (5.46 lower to 0.26 higher)	LOW	IMPORTANT
Discontinuation due to adverse events; 7 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	2/112 (1.8%)	5/113 (4.4%)	RR 0.4 (0.08 to 2.04)	27 fewer per 1000 (from 41 fewer to 46 more)	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 Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 86: Clinical evidence profile: atomoxetine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine versus placebo	Control	Relative (95% CI)	Absolute		
Quality of life (Child Health Questionnaire and Child Health and Illness Profile – Child edition); 0-100, higher values are beneficial; change scores reported; 6-10 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	281	110	-	SMD 0.72 higher (0.49 to 0.94 higher)	MODERATE	CRITICAL
Quality of life (KINDL-R); higher values are beneficial; 0-100; final values reported; 9 weeks												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	121	59	-	MD 7.9 higher (3.81 to 11.99 higher)	LOW	CRITICAL
Treatment response (defined as 25% reduction in ABC-H and CGI-I score of 1 or 2 and ≥25% decrease on ADHD-RS); 6-12 weeks												
2	randomised trials	serious ¹	Serious ²	no serious indirectness	no serious imprecision	none	63/80 (78.8%)	14/85 (16.5%)	RR 3.91 (1.54 to 9.89)	479 more per 1000 (from 89 more to 1000 more)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS, SNAP-IV and DSM-IV scale investigator rated total scores); lower values are beneficial, change scores reported; 6-9 weeks												
3	randomised trials	serious ¹	Serious ²	no serious indirectness	no serious imprecision	none	48	49	-	SMD 0.71 lower (1.35 to 0.07 lower)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS Investigator rated; SNAP-IV total scores); lower values are beneficial, final values reported; 6-13 weeks												
6	randomised	serious ¹	no serious	no serious	no serious	none	668	446	-	SMD 0.47 lower	MODERATE	CRITICAL

	trials		inconsistency	indirectness	imprecision					(0.75 to 0.18 lower)		
ADHD total symptoms teacher rated (multiple scales including ADHD-RS, SNAP-IV total scores; lower values are beneficial, change scores reported);6-9 weeks												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious ³	none	519	227	-	SMD 0.58 lower (0.74 to 0.42 lower)	MODERATE	CRITICAL
ADHD total symptoms teacher rated (ADHD-RS total scores; 0-54, lower values are beneficial) (Better indicated by lower values); 16 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	21	22	-	MD 4.66 lower (10.87 lower to 1.55 higher)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS total scores parent rated; CPRS total scores); lower values are beneficial; change scores;4-12 weeks												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1563	-	-	SMD 0.56 lower (0.68 to 0.45 lower)	HIGH	CRITICAL
ADHD total symptoms (ADHD-RS Parent rated total scores); 0-54, lower values are beneficial; final values; 8 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	36	36	-	MD 8.01 lower (12.1 to 3.92 lower)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS Parent rated total scores); 0-54, lower values are beneficial; 12-18 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	236	180	-	MD 6.98 lower (9.58 to 4.37 lower)	MODERATE	CRITICAL
ADHD inattentive symptoms (ADHD-RS Inattentive subscale Investigator rated); 0-27, lower values are beneficial; 6-9 weeks												
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	323	215	-	MD 3.49 lower (4.54 to 2.45 lower)	LOW	CRITICAL
ADHD inattentive symptoms (ADHD-RS inattentive subscale teacher rated); 0-27, Lower values are beneficial; 7-12 weeks												
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	393	190	-	MD 2.77 lower (4.07 to 1.47 lower)	LOW	CRITICAL
ADHD inattentive symptoms (ADHD-RS inattentive subscale teacher rated); 0-27, Lower values are beneficial; 16 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	none	21	22	-	MD 4.16 lower (7.64 to 0.68 lower)	LOW	CRITICAL
ADHD inattentive symptoms (ADHD-RS and CPRS Inattentive subscales parent rated; lower values are beneficial, change scores reported); 4-12 weeks												

9	randomised trials	serious ¹	Serious ²	no serious indirectness	no serious imprecision	none	1563	-	-	SMD 0.61 lower (0.79 to 0.43 lower)	LOW	CRITICAL
ADHD inattentive symptoms parent rated (ADHD-RS inattention subscale; 0-27, low values are beneficial, final values reported); 4 weeks												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	36	36	-	MD 4.06 lower (6.17 to 1.95 lower)	LOW	CRITICAL
ADHD inattention symptoms (ADHD-RS Parent rated inattention subscale); 0-27, lower values are beneficial; 12 – 18 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	294	211	-	MD 3.6 lower (4.71 to 2.49 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS hyperactive subscale investigator rated); 0-27, lower values are beneficial; 6-9 weeks												
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	323	215	-	MD 4.87 lower (5.95 to 3.78 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS hyperactive subscale teacher rated); 0-27, lower values are beneficial; 4-12 weeks												
4	randomised trials	no serious risk of bias	Serious ²	no serious indirectness	no serious imprecision	none	396	196	-	MD 2.53 lower (4.01 to 1.05 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS hyperactive subscale teacher rated); 0-27, lower values are beneficial; 16 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	none	21	22	-	MD 0.51 lower (4.62 lower to 3.6 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS and CPRS hyperactive subscale parent rated; lower values are beneficial, change scores reported); 4-12 weeks												
9	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	1563	-	-	SMD 0.6 lower (0.78 to 0.42 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms parent rated (ADHD-RS hyperactivity subscale; 0-27, low values are beneficial, final values reported); 4 weeks												
2	randomised trials	very serious ¹	Serious ²	no serious indirectness	no serious imprecision	none ¹	36	36	-	MD 4.16 lower (9.03 to 0.72 lower)	VERY LOW	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS Parent rated hyperactivity subscale); 0-27, lower values are beneficial; 12-18 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	195	144	-	MD 2.89 lower (4.2 to 1.58 lower)	MODERATE	CRITICAL

CGI score of 1 or 2; 4-13 weeks												
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	134/294 (45.6%)	78/287 (27.2%)	RR 1.68 (1.35 to 2.09)	185 more per 1000 (from 95 more to 296 more)	MODERATE	CRITICAL
Behavioural measures (ABC-H, CPRS oppositional subscale); lower values are beneficial, change scores reported; 6-12 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	309	115	-	SMD 0.32 lower (0.54 to 0.11 lower)	LOW	IMPORTANT
Behavioural measures (SNAP-IV ODD subscale, CPRS oppositional subscale), lower values are beneficial, final values reported; 6-12 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	164	116	-	SMD 0.31 lower (0.55 to 0.06 lower)	MODERATE	IMPORTANT
CHIP-PRF Achievement subscale; 0-30; high values are beneficial; 12 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	99	50	-	MD 3.39 higher (0.66 lower to 7.44 higher)	LOW	IMPORTANT
Discontinuation due to adverse events; 3-10 weeks												
16	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	61/1620 (3.8%)	32/968 (3.3%)	OR 1.35 (0.87 to 2.11)	11 more per 1000 (from 4 fewer to 34 more)	MODERATE	CRITICAL
Discontinuation due to adverse events; 12-18 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	3/163 (1.8%)	2/161 (1.2%)	RR 1.47 (0.25 to 8.71)	6 more per 1000 (from 9 fewer to 84 more)	LOW	CRITICAL
Serious adverse events; 6-10 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	1/255 (0.39%)	0/95 (0%)	RD 0 (-0.02 to 0.03)	0 more per 1000 (from 2 fewer to 3 more)	LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgraded due to heterogeneity, unexplained by subgroup analysis

³ Downgraded by 1 increment if the confidence interval crossed one MID.

⁴ Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 87: Clinical evidence profile: atomoxetine versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine versus methylphenidate	Control	Relative (95% CI)	Absolute		
Quality of life (Child Health Questionnaire); 0-100, higher values are beneficial, final values reported; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	72	75	-	MD 0.1 higher (3.67 lower to 3.87 higher)	MODERATE	CRITICAL
ADHD total symptoms parent rated (ADHD symptoms – CRPS, ADHD-RS); lower values are beneficial; 6-8 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	240	240	-	SMD 0.13 higher (0.05 lower to 0.31 higher)	MODERATE	CRITICAL
ADHD inattention symptoms parent rated (ADHD-RS and CPRS inattention subscales); 0-27, lower values are beneficial; 6-8 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	244	246	-	SMD 0.14 higher (0.03 lower to 0.32 higher)	MODERATE	CRITICAL
ADHD hyperactivity symptoms parent rated (ADHD-RS and CPRS hyperactivity subscale); 0-27, lower values are beneficial; 6-8 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	244	246	-	SMD 0 higher (0.18 lower to 0.18 higher)	MODERATE	CRITICAL
Behavioural outcomes (CPRS Oppositional subscale); 0-18, lower values are beneficial; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	162	164	-	MD 0.4 higher (0.47 lower to 1.27 higher)	MODERATE	IMPORTANT
Discontinuation due to adverse events; 8 weeks												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/164 (11%)	6/166 (3.6%)	RR 3.04 (1.24 to 7.46)	74 more per 1000 (from 9 more to 233 more)	MODERATE	CRITICAL
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¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

Table 88: Clinical evidence profile: atomoxetine versus guanfacine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine versus Guanfacine ER	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54; lower values are beneficial, change scores reported (Better indicated by lower values); 10-13 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	111	114	-	MD 8.9 higher (5.57 to 12.23 higher)	LOW	CRITICAL
Treatment response (CGI-I score of 1 or 2); 10-13 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	63/112 (56.3%)	76/114 (66.7%)	RR 0.84 (0.68 to 1.04)	107 fewer per 1000 (from 213 fewer to 27 more)	LOW	CRITICAL
Discontinuation due to adverse events; 10-13 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	5/112 (4.5%)	9/115 (7.8%)	RR 0.57 (0.2 to 1.65)	34 fewer per 1000 (from 63 fewer to 51 more)	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 Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 89: Clinical evidence profile: guanfacine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guanfacine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (investigator, ADHD-RS total scores); 0-54, lower values are beneficial; 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 8.1 lower (16.47 lower to 0.27 higher)	MODERATE	CRITICAL
ADHD inattention symptoms (investigator, ADHD-RS Inattentive subscale); 0-27, lower values are beneficial; 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 2.6 lower (6.88 lower to 1.68 higher)	MODERATE	CRITICAL
ADHD total symptoms (investigator, ADHD-RS hyperactive subscale); 0-27, lower values are beneficial; 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 5.5 lower (10.95 to 0.05 lower)	MODERATE	CRITICAL
CGI-I at 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/17 (52.9%)	0/17 (0%)	OR 14.01 (3.12 to 62.88)	530 mre per 1000 (from 290 more to 770 more)	HIGH	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

Table 90: Clinical evidence profile: extended release guanfacine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ER Guanfacine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD symptoms investigator rated (ADHD-RS); 0-54, Lower values are beneficial; change scores reported; 5-13 weeks												
6	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	0	-	-	MD 6.6 lower (7.98 to 5.23 lower)	LOW	CRITICAL
ADHD inattention symptoms investigator rated (ADHD-RS Inattentive subscale); 0-27, Lower values are beneficial, change scores and final values reported; 6-8 weeks												
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	523	355	-	MD 4.02 lower (5.19 to 2.85 lower)	LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated (ADHD-RS Hyperactive/impulsive subscale); 0-54, lower values are beneficial, change scores reported; 6-8 weeks												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	493	323	-	MD 3.87 lower (5.32 to 2.43 lower)	HIGH	CRITICAL
ADHD hyperactivity symptoms investigator rated (Aberrant Behaviour Checklist – Hyperactivity); 0-100, Lower values are beneficial, final values reported; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision ¹	none	30	32	-	MD 8.1 lower (10.95 to 5.25 lower)	MODERATE	CRITICAL
CGI-I at 5-13 weeks												
5	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	435/782 (55.6%)	113/352 (32.1%)	RR 1.8 (1.52 to 2.14)	257 more per 1000 (from 167 more to 366 more)	MODERATE	CRITICAL
Academic outcome (Weiss Functional Impairment Rating Scale Academic Performance subscale; 0-3; low scores are beneficial) (Better indicated by lower values); 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	333	-	-	SMD 0.34 lower (0.54 to 0.14 lower)	HIGH	BEHAVIOUR
Discontinuation due to adverse events; 5-13 weeks												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/1299 (8.8%)	11/700 (1.6%)	OR 3.26 (2.18 to 4.87)	34 more per 1000 (from 18 more to 56 more)	HIGH	CRITICAL
Serious adverse events; 8 weeks												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ¹	none	1/30 (3.3%)	0/32 (0%)	OR 7.9 (0.16 TO 398.8)	3 more per 1000 (from 50 fewer to 120 more)	VERY LOW	CRITICAL
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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 Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 91: Clinical evidence profile: Clonidine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms parent rated (ASQ-P total scores; 0-20; lower values are beneficial); 16 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	127	-	-	MD 3.04 lower (5.18 to 0.91 lower)	LOW	CRITICAL
ADHD total symptoms teacher rated (ASQ-T total scores); 0-20; lower values are beneficial; 16 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	126	-	-	MD 2.21 lower (4.76 lower to 0.33 higher)	LOW	CRITICAL
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, lower values are beneficial; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	158	78	-	MD 8.56 lower (11.5 to 5.62 lower)	LOW	CRITICAL
ADHD inattention symptoms investigator rated (ADHD-RS inattention subscale); 0-27, lower values are beneficial, change scores reported; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	152	76	-	MD 4.3 lower (6.16 to 2.44 lower)	LOW	CRITICAL

ADHD hyperactivity symptoms (Mother/Teacher CBCL Hyperactivity subscale); 0-100, lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	34	-	MD 5.1 lower (5.63 to 4.57 lower)	HIGH	CRITICAL
ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactivity scores); 0-27, lower values are beneficial, change scores reported; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	152	76	-	MD 4.52 lower (6.45 to 2.59 lower)	LOW	CRITICAL
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial; 16 weeks												
2	randomised trials	Very serious ²	no serious inconsistency	no serious indirectness	Serious ³	none	126	-	-	MD 10.78 higher (5.93 to 15.64 higher)	VERY LOW	IMPORTANT
Discontinued due to adverse events; 16 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	21/185 (11.4%)	1/65 (1.5%)	OR 3 (0.98 to 9.15)	29 more per 1000 (from 0 fewer to 110 more)	MODERATE	CRITICAL
Serious adverse events; 16 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	0/158 (0%)	0/78 (0%)	RD 0 (-0.02 to 0.02)	-	HIGH	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 evidence was at very high risk of bias

³ Downgraded by 1 increment if the confidence interval crossed one MID.

Table 92: Clinical evidence profile: Clonidine versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD total symptoms teacher rated (Conners ASQ-T total scores); 0-20; lower values are beneficial, change scores reported (Better indicated by lower values); 16 weeks												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	31	29	-	MD 1.72 higher (1.48 lower to 4.92 higher)	VERY LOW	CRITICAL
ADHD total symptoms parent rated (Conners ASQ-P total scores); 0-20; lower values are beneficial, change scores reported (Better indicated by lower values); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	31	29	-	MD 2.5 higher (1 lower to 6 higher)	VERY LOW	CRITICAL
Behavioural outcomes (Children's Global Assessment Scale) 0-100, higher values are beneficial (Better indicated by lower values); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	-	-	MD 3.6 lower (9 lower to 1.8 higher)	MODERATE	IMPORTANT
Discontinued due to adverse events; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/31 (3.2%)	1/29 (3.4%)	RR 0.94 (0.06 to 14.27)	2 fewer per 1000 (from 32 fewer to 458 more)	VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 93: Clinical evidence profile: Clonidine versus desipramine

Quality assessment							No of patients			Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine versus desipramine	Control	Relative (95% CI)	Absolute			
Mother/Teacher CBCL Hyperactivity subscale (Better indicated by lower values); 6 weeks													
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	34	-	MD 2.1 higher (1.48 to 2.72 higher)	HIGH	CRITICAL	

Table 94: Clinical evidence profile: Clonidine versus carbamazepine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine verses carbamazepine	Control	Relative (95% CI)	Absolute		
Treatment response – Inattention; 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	3/9 (33.3%)	2/13 (15.4%)	RR 2.17 (0.45 to 10.46)	180 more per 1000 (from 85 fewer to 1000 more)	VERY LOW	CRITICAL
Treatment response – Hyperactivity; 4 weeks												
1	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/21 (85.7%)	3/19 (15.8%)	RR 5.43 (1.89 to 15.56)	699 more per 1000 (from 141 more to 1000 more)	LOW	CRITICAL
Treatment response – Impulsivity; 4 weeks												
1	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/18 (83.3%)	4/17 (23.5%)	RR 3.54 (1.47 to 8.55)	598 more per 1000 (from 111 more to 1000 more)	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.

³ Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 95: Clinical evidence profile: Desipramine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Desipramine versus placebo	Control	Relative (95% CI)	Absolute		

ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, Lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	20	-	MD 18 lower (24.05 to 11.95 lower)	HIGH	CRITICAL
Mother/Teacher CBCL Hyperactivity subscale (Better indicated by lower values); 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	34	-	MD 7 lower (7.58 to 6.42 lower)	HIGH	CRITICAL

Table 96: Clinical evidence profile: Venlafaxine versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (ADHD-RS total scores parent rated); 0-54, Lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	19	19	-	MD 2.48 higher (2.51 lower to 7.47 higher)	MODERATE	CRITICAL
ADHD total symptoms (ADHD-RS total scores teacher rated); 0-54, Lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	19	19	-	MD 2.26 higher (1.98 lower to 6.5 higher)	MODERATE	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID..

Table 97: Clinical evidence profile: Risperidone versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risperidone versus placebo	Control	Relative (95% CI)	Absolute		
ADHD inattention symptoms (8 weeks PT; parent rated; CPRS; 0-3; high is poor); 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	42	42	-	MD 0.23 lower (0.36 to 0.1 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms (8 weeks PT; parent rated; CPRS; 0-3; high is poor); 8 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	42	42	-	MD 0.05 lower (0.15 lower to 0.05 higher)	MODERATE	CRITICAL
Behaviour outcomes (ABC and CPRS oppositional subscale); 8-10 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	61	61	-	SMD 0.63 lower (0.99 to 0.26 lower)	MODERATE	IMPORTANT
Children's Global Assessment Scale (0-100, higher values are beneficial); 24 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	19	20	-	MD 5.74 higher (0.33 to 11.15 higher)	MODERATE	IMPORTANT
Serious adverse events; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	0/19 (0%)	1/19 (5.3%)	OR 0.14 (0 to 6.82)	45 fewer per 1000 (from 53 fewer to 222 more)	LOW	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 98: Clinical evidence profile: Aripiprazole versus placebo

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aripiprazole versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms parent rated (SNAP-IV); 0-3, lower values are beneficial												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	17	24	-	MD 0.24 higher (0.3 lower to 0.78 higher)	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 99: Clinical evidence profile: Buspirone versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buspirone versus methylphenidate	Control	Relative (95% CI)	Absolute		
Treatment response (Defined as ≥30% reduction in ADHD-RS); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	14/18 (77.8%)	14/16 (87.5%)	RR 0.89 (0.65 to 1.21)	96 fewer per 1000 (from 306 fewer to 184 more)	VERY LOW	CRITICAL
ADHD total symptoms (ADHD-RS Parent rated); 0-54, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	20	20	-	MD 6.65 higher (1.52 to 11.78 higher)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS Parent rated); 0-54, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 12.6 higher (7.27 to 17.93 higher)	MODERATE	CRITICAL

Discontinuation due to adverse events; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	1/18 (5.6%)	0/16 (0%)	OR 6.61 (0.13 to 335.5)	-	VERY LOW	CRITICAL
Serious adverse events; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/18 (0%)	0/16 (0%)	RD 0 (-0.11 to 0.11)	0 events in both arms	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.

³ Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 100: Clinical evidence profile: Bupropion versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms parent rated (Conners Abbreviated Parent Questionnaire and CPTQ-P); lower values are beneficial, final values reported); 4-6 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	44	-	SMD 0.63 lower (1.01 to 0.25 lower)	MODERATE	CRITICAL
ADHD total symptoms teacher rated (Conners Abbreviated Teacher Questionnaire and CPTQ-T); lower values are beneficial, final values reported); 4-6 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	72	37	-	SMD 0.7 lower (1.11 to 0.29 lower)	MODERATE	CRITICAL
Discontinuation due to adverse events; 4-6 weeks												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	5/92 (5.4%)	0/47 (0%)	OR 4.69 (0.72 to 30.55)	-	LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 101: Clinical evidence profile: Bupropion versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (PT; ADHD-RS Parent rated); 0-54, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	20	20	-	MD 1.4 higher (3.38 lower to 6.18 higher)	LOW	CRITICAL
ADHD total symptoms parent rated (Iowa Conners rating scale; crossover trial; 0-30; lower values are beneficial); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	15	15	-	MD 3 higher (0.76 lower to 6.76 higher)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial, change scores PT; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	20	20	-	MD 0.5 lower (6.42 lower to 5.42 higher)	LOW	CRITICAL
ADHD total symptoms teacher rated (Iowa Conners rating scale; crossover trial, final values; 0-30; lower values are beneficial); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	15	15	-	MD 3 higher (1.37 lower to 7.37 higher)	LOW	CRITICAL
ADHD inattention symptoms (ADHD-RS Inattention subscale - Parent rated); 0-27, lower values are beneficial; change score; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	20	20	-	MD 1 higher (1.32 lower to 3.32 higher)	LOW	CRITICAL

ADHD inattention symptoms parent rated (Iowa Conners rating scale inattention subscale; crossover trial final values; 0-15; lower values are beneficial); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	15	15	-	MD 2.4 higher (0.75 to 4.05 higher)	LOW	CRITICAL
ADHD inattention symptoms (ADHD-RS Inattention subscale - Teacher rated); 0-27, lower values are beneficial, change scores; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	20	20	-	MD 0.4 lower (4.03 lower to 3.23 higher)	LOW	CRITICAL
ADHD inattention symptoms teacher rated (Iowa Conners rating scale inattention subscale; crossover trial final values; 0-15; lower values are beneficial); 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	15	15	-	MD 1.9 higher (0.75 lower to 4.55 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Parent rated); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	20	20	-	MD 0.6 higher (2.58 lower to 3.78 higher)	VERY LOW	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Teacher rated); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	20	20	-	MD 0.1 lower (3.17 lower to 2.97 higher)	LOW	CRITICAL
Discontinuation due to adverse events; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	0/20 (0%)	0/20 (0%)	RD 0.00 (-0.09 to 0.09)	0 events in both arms	LOW	CRITICAL
Serious adverse events; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	0/20 (0%)	0/20 (0%)	RD 0.00 (-0.09 to 0.09)	0 events in both arms	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 Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 102: Clinical evidence profile: Modafinil versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (ADHD-RS Parent rated); 0-54, lower values are beneficial, change scores reported; 5 weeks												
1	randomised trials	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	23	-	MD 14.26 lower (18.69 to 9.83 lower)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS Teacher rated); 0-54, lower values are beneficial, final values reported; 5-6 weeks												
2	randomised trials	serious ¹	Serious ²	no serious indirectness	no serious imprecision	none	34	34	-	MD 8.17 lower (22.74 lower to 6.4 higher)	LOW	CRITICAL
CGI-I; 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	45/147 (30.6%)	9/51 (17.6%)	RR 1.73 (0.91 to 3.29)	129 more per 1000 (from 16 fewer to 404 more)	LOW	CRITICAL
Serious adverse events; 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	0/197 (0%)	0/51 (0%)	RD 0 (-0.03 to 0.03)	0 events in both arms	LOW	CRITICAL
Discontinuation due to adverse events; 4 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	9/197 (4.6%)	0/51 (0%)	OR 3.67 (0.71 to 19)	-	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 due to heterogeneity, unexplained by subgroup analysis

³ Downgraded by 1 increment if the confidence interval crossed one MID.

⁴ Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 103: Clinical evidence profile: modafinil versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (ADHD-RS total scores Parent rated); 0-54, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	30	30	-	MD 1.7 lower (8.46 lower to 5.06 higher)	LOW	CRITICAL
ADHD total symptoms (ADHD-RS total scores Teacher rated); 0-54, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	30	30	-	MD 0.8 higher (4.23 lower to 5.83 higher)	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 104: Clinical evidence profile: melatonin versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin versus placebo	Control	Relative (95% CI)	Absolute		
TNO-AZL Questionnaire for Children's Health-Related Quality of Life (higher values are beneficial); 4 weeks												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	52	-	MD 2.2 higher (6.28 lower to 10.68 higher)	HIGH	CRITICAL
Behavioural outcomes (Teachers Report Form); 0-100, lower values are beneficial, final values reported; 4 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	53	52	-	MD 6 lower (14.52 lower to 2.52 higher)	MODERATE	IMPORTANT
Discontinuation due to adverse effects; 4 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	0/53 (0%)	0/52 (0%)	RD 0 (-0.04 to 0.04)	0 events in both arms	MODERATE	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

Table 105: Clinical evidence profile: amantadine versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amantadine versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD inattention symptoms (ADHD-RS Inattention subscale - Parent rated); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	19	19	-	MD 0.4 higher (4.1 lower to 4.9 higher)	LOW	CRITICAL
ADHD inattention symptoms (ADHD-RS Inattention subscale - Teacher rated); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	19	19	-	MD 0.2 higher (2.5 lower to 2.9 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Parent rated); 0-27, lower values are beneficial; 6 weeks												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	19	19	-	MD 0.6 higher (3.36 lower to 4.56 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms (ADHD-RS Hyperactivity subscale - Teacher rated); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none ¹	19	19	-	MD 0.2 lower (3.54 lower to 3.14 higher)	LOW	CRITICAL

¹ Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 106: Clinical evidence profile: methylphenidate and clonidine versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate and clonidine versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD total symptoms; teacher rated (Conners ASQ-T total scores; 0-20; low values are beneficial); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	29	-	MD 2.21 lower (5.9 lower to 1.48 higher)	MODERATE	CRITICAL
ADHD total symptoms; parent rated (Conners ASQ-P total scores; 0-20; low values are beneficial); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	32	29	-	MD 3 lower (6.4 lower to 0.4 higher)	VERY LOW	CRITICAL
Behaviour (CGAS; 0-100; higher scores are beneficial); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	61	-	-	MD 2.7 higher (2.6 lower to 8 higher)	VERY LOW	IMPORTANT
Discontinued due to adverse events; 16 weeks												
1	randomised	no serious	no serious	no serious	very serious ²	none	3/32	1/29	RR 2.72	59 more per	LOW	CRITICAL

	trials	risk of bias	inconsistency	indirectness			(9.4%)	(3.4%)	(0.3 to 24.7)	1000 (from 24 fewer to 817 more)		
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¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 107: Clinical evidence profile: methylphenidate and clonidine versus clonidine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylphenidate and clonidine versus clonidine	Control	Relative (95% CI)	Absolute		
ADHD total symptoms; teacher rated (Conners ASQ-T total scores; 0-20; low values are beneficial); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ¹	none	32	30	-	MD 4.08 lower (7.65 to 0.51 lower)	VERY LOW	CRITICAL
Behavioural outcome (CGAS; 0-100; higher scores are beneficial); 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ¹	none	63	-	-	MD 0.9 lower (6.2 lower to 4.4 higher)	VERY LOW	IMPORTANT
Discontinued due to adverse events; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ¹	none	3/32 (9.4%)	0/30 (0%)	OR 7.41 (0.74 to 74.11)	-	VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 108: Clinical evidence profile: methylphenidate and clonidine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyphenidate and clonidine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD symptoms; teacher rated (Conners ASQ-T; 0-20; low values are beneficial); 16 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	32	31	-	MD 5.38 lower (7.89 to 2.87 lower)	LOW	
ADHD symptoms; parent rated (Conners ASQ-P; 0-20; low values are beneficial); 16 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	32	31	-	MD 5.44 lower (8.44 to 2.43 lower)	LOW	
Discontinued due to adverse events; 16 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ¹	none	3/32 (9.4%)	1/31 (3.2%)	RR 2.91 (0.32 to 26.46)	62 more per 1000 (from 22 fewer to 821 more)	VERY LOW	

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 Downgrade by 2 increments if the confidence interval crossed both MIDs.

4

Table 109: Clinical evidence: atomoxetine and fluoxetine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine and fluoxetine versus atomoxetine and placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms; investigator rated (ADHD-RS total scores); 0-54; low values are beneficial; 8 weeks												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	113	44	-	MD 3.5 lower (8.06 lower to 1.06 higher)	VERY LOW	CRITICAL
ADHD inattention symptoms; investigator rated rated (ADHD-RS inattention subscale); 0-27; low values are beneficial; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	113	44	-	MD 2.2 lower (4.71 lower to 0.31 higher)	VERY LOW	CRITICAL
ADHD hyperactivity symptoms; investigator rated rated (ADHD-RS hyperactivity subscale); 0-27; low values are beneficial; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	113	44	-	MD 1.2 lower (3.61 lower to 1.21 higher)	VERY LOW	CRITICAL
Discontinued due to adverse events; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	3/127 (2.4%)	1/46 (2.2%)	RR 1.09 (0.12 to 10.19)	2 more per 1000 (from 19 fewer to 200 more)	VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

F.1.3 Adults

Table 110: Clinical evidence profile: Immediate release methylphenidate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate release methylphenidate versus placebo	Control	Relative (95% CI)	Absolute		
Treatment response (follow-up 3-6 weeks)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	76/123	9/77	RR 4.45 (2.4 to 8.25)	403 more per 1000 (from 164 more to 847)	MODERATE	CRITICAL

										more)		
ADHD symptoms - Final values (follow-up 3-4 weeks; Better indicated by lower values)												
2	randomised trials	serious ¹	Serious ³	no serious indirectness	no serious imprecision	none	54	54	-	SMD 0.34 higher (0.98 lower to 0.29 higher)	LOW	CRITICAL
ADHD symptoms - Change scores (follow-up 7 weeks; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	8	11	-	MD 2.3 higher (6.2 lower to 10.8 higher)	VERY LOW	CRITICAL
CGI score of 1 or 2 (follow-up 7 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/31	4/34	-	638 more per 1000 (from 154 fewer to 1000 more)	MODERATE	CRITICAL
Behavioural outcomes (follow-up 2-4 weeks; Better indicated by lower values)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	67	-	SMD 1.01 higher (0.65 to 1.37 higher)	MODERATE	IMPORTANT
Discontinued due to adverse events (follow-up 3-7 weeks)												
2	randomised trials	no serious risk of bias	No serious inconsistency	no serious indirectness	no serious imprecision	none	2/53 (3.8%)	1/56 (1.8%)	RD 0.04 (-0.18 to 0.27)	73 more per 1000 (from 20 more to 130 more)	HIGH	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgrade by 2 increments if the confidence interval crossed both MIDs.

³Downgraded due to heterogeneity, unexplained by subgroup analysis

Table 111: Clinical evidence profile: OROS methylphenidate versus placebo

Quality assessment	No of patients	Effect	Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Controlled release methylphenidate versus placebo	Control	Relative (95% CI)	Absolute		
Treatment response (defined as CGI-I of 1 or 2 and 30% reduction on AISRS and 30% reduction on WRAADDs); 6-8 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/234	52/240	RR 2.2 (1.52 to 2.57)	302 more per 1000 (from 188 more to 443 more)	MODERATE	CRITICAL
ADHD total symptoms investigator rated (CAARS-O:SV total scores); 0-54, lower values are beneficial, change scores reported; 5-13 weeks												
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	770	484	-	SMD 0.38 lower (0.5 to 0.27 lower)	LOW	CRITICAL
ADHD total symptoms(AISRS/ADHD-RS total scores); lower values are beneficial, final values reported; 5-8 weeks												
2	randomised trials	no serious risk of bias	serious ²	no serious indirectness	no serious imprecision	none	24	26	-	SMD 0.91 lower (1.28 to 0.53 lower)	MODERATE	CRITICAL
ADHD symptoms - Self-rated (follow-up mean 2-5 weeks; Better indicated by lower values); 2-5 weeks												
2	randomised trials	no serious risk of bias	Serious ²	no serious indirectness	no serious imprecision	none	24	26	-	SMD 0.94 lower (2.06 to 0.19 lower)	MODERATE	CRITICAL
ADHD total symptoms self rated (CAARS-O:SV and CAARS ADHD index total scores); lower values are beneficial, final values reported; 5-6 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	482	275	-	MD 6.15 lower (8.3 to 3.99 lower)	LOW	CRITICAL
ADHD total symptoms self rated (CAARS total scores); 0-54, lower values are beneficial, change scores reported; 13 weeks												
1	randomised trials	serious	no serious inconsistency	no serious indirectness	Serious ³	none	182	97		MD 4.2 lower (7.24 lower to 1.16 lower)	LOW	CRITICAL
ADHD inattention symptoms investigator rated (CAARS Inattention subscale); lower values are beneficial, change scores reported; 5 weeks												
1	randomised	serious ¹	no serious	no serious	Serious ³	none	302	96	-	MD 3 lower (4.24	LOW	CRITICAL

	trials		inconsistency	indirectness							to 1.76 lower)		
ADHD inattention symptoms investigator rated (CAARS Inattention subscale, ADHD-RS inattention subscale); lower values are beneficial, final values reported; 3-8 weeks													
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	56	58			SMD 0.66 (1.04 lower to 0.28 lower)	MODERATE	CRITICAL
ADHD inattention symptoms investigator rated (CAARS Inattention subscale); lower values are beneficial, change scores reported; 13 weeks													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	304	96	-		MD 2.4 lower (4.03 lower to 0.01 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated (CAARS Hyperactive subscale); 0-27; lower values are beneficial, change scores reported; 5 weeks													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	304	96	-		MD 1.3 lower (2.61 lower to 0.01 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated (CAARS and ADHD-RS hyperactivity subscales); lower values are beneficial, change scores reported; 2-8 weeks													
2	randomised trials	No serious risk of bias	Serious ²	no serious indirectness	Serious ³	none	56	58			SMD 0.41 (1.06 lower to 0.25 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated (CAARS Hyperactive subscale); lower values are beneficial, change scores; 13 weeks													
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	182	97			MD 1.3 lower (2.7 lower to 0.1 higher)	LOW	CRITICAL
CGI score of 1 or 2 (follow-up 8 weeks); 7-13 weeks													
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/234	52/240	RR 2.02 (1.52 to 2.67)		220 more per 1000 (from 140 more to 300 more)	HIGH	CRITICAL
Global Assessment of Functioning (follow-up 5 weeks; Better indicated by lower values)													
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15	15	-		MD 15.8 higher (8.17 to 23.43 higher)	HIGH	IMPORTANT

CAARS-S:L Emotional Liability Scale (follow-up 5 weeks; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	241	118	-	MD 1.3 lower (2.29 TO 0.31 lower)	VERY LOW	IMPORTANT
WRAADDs Emotional Dysregulation subscale (better indicated by lower values); 4 weeks												
1	randomised trials	No serious risk of bias	no serious inconsistency	no serious indirectness	Serious ³	none	47	47		MD 6.5 lower (9.68 lower to 3.32 lower)	MODERATE	IMPORTANT
Discontinued due to adverse events at 6-13 weeks												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	107/1176	23/824	OR 3.02 (2.08 to 4.38)	52 more per 1000 (from 28 more to 84 more)	HIGH	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgraded by 1 increment due to heterogeneity, unexplained by subgroup analysis.

³ Downgrade by 2 increments if the confidence interval crossed both MIDs.

Table 112: Clinical evidence profile: Dexamphetamine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamphetamine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD symptoms (follow-up 6-7 weeks; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	38	38	-	MD 7.71 lower (12.63 to 2.79 lower)	MODERATE	CRITICAL
ADHD symptoms inattentive subscale (follow-up 6-7 weeks; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	38	38	-	MD 4.53 lower (7.07 to 2 lower)	MODERATE	CRITICAL

ADHD symptoms Hyperactive subscale (follow-up 6-7 weeks; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	38	38	-	MD 3.11 lower (5.93 to 0.3 lower)	MODERATE	CRITICAL
CGI-I score of 1 or 2 (follow-up 6 weeks)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/24 (58.3%)	0/21 (0%)	OR 14.31 (4.1 to 50.01)	-	MODERATE	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

² Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

Table 113: Clinical evidence profile: Lisdexamfetamine dimesylate versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lisdexamfetamine dimesylate versus placebo	Control	Relative (95% CI)	Absolute		
Quality of life (AAQoL); 0-100, higher values are beneficial at 10 weeks												
1	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	Serious ³	none	102	60	-	MD 14.70 higher (5.90 to 23.50 higher)	VERY LOW	IMPORTANT
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54, lower values are beneficial, change scores reported; 4-10 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	389	92	-	MD 10.51 lower (12.71 to 8.31 lower)	MODERATE	CRITICAL
ADHD inattention symptoms investigator rated;(ADHD-RS inattention subscale); 0-27, lower values are beneficial; 10 weeks												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	74	-	MD 6.1 lower (8.26 to 3.94 lower)	LOW	CRITICAL

ADHD hyperactivity symptoms investigator rated (ADHD-RS hyperactivity subscale); 0-27, lower values are beneficial; 10 weeks												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	74	-	MD 5 lower (6.8 to 3.2 lower)	LOW	CRITICAL
CGI score of 1 or 2 (follow-up 4 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	207/358	18/62	RR 1.99 (1.34 to 2.97)	287 more per 1000 (from 99 more to 572 more)	MODERATE	CRITICAL
Behavioural outcomes (global assessment of functioning); 0-100, high values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	31	30	-	MD 4.6 higher (2.29 to 6.91 higher)	LOW	IMPORTANT
Discontinuation due to adverse events (follow-up 4-6 weeks)												
3	randomised trials	Serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	22/332 (6.6%)	4/190 (2.1%)	OR 2.55 (1.12 to 5.82)	31 more per 1000 (from 2 more to 90 more)	LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgraded by 2 increment if the majority of the evidence was at very high risk of bias.

³ Downgraded by 1 increment if the confidence interval crossed one MID.

4

Table 114: Clinical evidence profile: Atomoxetine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atomoxetine versus placebo	Control	Relative (95% CI)	Absolute		
Quality of life (AAQoL); 0-100; higher values are beneficial 10-12 weeks												

3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	449	457	-	MD 4.72 higher (2.66 to 6.77 higher)	MODERATE	CRITICAL
Quality of life (AAQoL); 0-100; higher values are beneficial 16-24 weeks												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	318	330	-	MD 4.04 higher (1.55 to 6.54 higher)	LOW	CRITICAL
ADHD total symptoms (multiple scales including AISRS and ADHD-RS total scores; Investigator rated); lower values are beneficial, change scores reported; 8-12 weeks												
5	randomised trials	very serious ¹	Serious ³	no serious indirectness	Serious ⁴	none	-	-	-	SMD 0.7 lower (1.07 to 0.33 lower)	VERY LOW	CRITICAL
ADHD total symptoms (CAARS and AISRS total scores; Investigator rated); lower values are beneficial, final values reported; 8-12 weeks												
2	randomised trials	serious ¹	Serious ³	no serious indirectness	Serious ⁴	none	286	244	-	SMD (0.82 lower (1.8 to 0.16 lower)	VERY LOW	CRITICAL
ADHD total symptoms investigator rated (CAARS and AISRS total score; Investigator rated); 0-54, lower values are beneficial; 16-24 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ⁴	none	731	698	-	SMD 0.37 lower (0.47 to 0.27 lower)	LOW	CRITICAL
ADHD total symptoms (CAARS total score - Self rated); 0-84, lower values are beneficial, change scores reported; 10-12 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ⁴	none	411	420	-	MD 4.83 lower (6.27 lower to 3.39 lower)	LOW	CRITICAL
ADHD inattention symptoms (CAARS Inattention subscale - Self rated); 0-27, lower values are beneficial, change scores reported; 10-12 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ⁴	none	411	420	-	MD 2.53 lower (3.33 to 1.72)	LOW	CRITICAL
ADHD inattention symptoms (multiple scales including CAARS inattention subscale - Investigator rated); 0-27; lower values are beneficial, change scores reported; 8-12 weeks												
6	randomised trials	very serious ²	Serious ³	no serious indirectness	Serious ⁴	none	1763		-	SMD 0.44 lower (0.61 to 0.26 lower)	VERY LOW	CRITICAL
ADHD inattention symptoms (CAARS and AISRS Inattention subscale - Investigator rated); 0-27, lower values are beneficial; 16-24 weeks												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ⁴	none	534	510	-	SMD 0.37 lower (0.6 to 0.14 lower)	LOW	CRITICAL

ADHD hyperactivity symptoms (CAARS and AISRS Hyperactivity/impulsivity subscale - Investigator rated); lower values are beneficial, change scores reported; 8-12 weeks												
6	randomised trials	Very serious ²	no serious inconsistency	no serious indirectness	very serious ⁵	none	1763		-	SMD 0.38 lower (0.48 to 0.28 lower)	VERY LOW	CRITICAL
ADHD hyperactivity symptoms (CAARS Hyperactivity/impulsivity subscale - Self rated); lower values are beneficial, change scores reported; 10-12 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	411	420	-	MD 2.21 lower (2.83 to 1.29 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms (AISRS and CAARS Hyperactivity/impulsivity subscale - Investigator rated); lower values are beneficial at 16 to 24 weeks; 16-24 weeks												
3	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	Serious ⁵	none	534	510	-	SMD 0.34 lower (0.34 to 0.22 lower)	VERY LOW	CRITICAL
BRIEF-A Self Report total score (Better indicated by lower values); 10-12 weeks												
2	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	362	-	MD 4.92 lower (7.1 to 2.73 lower)	LOW	IMPORTANT
Discontinuation due to adverse events (follow-up 8-14 weeks)												
7	randomised trials	Serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/885	28/844	OR 2.3 (1.53 to 3.47)	40 more per 1000 (from 17 more to 73 more)	MODERATE	CRITICAL
Discontinuation due to adverse events (follow-up 24 weeks)												
1	randomised trials	Serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/268	22/234	RR 2.26 (1.43 to 3.58)	118 more per 1000 (from 40 more to 243 more)	MODERATE	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgraded by 2 increment if the majority of the evidence was at very high risk of bias.

³ Downgraded by 1 increment due to heterogeneity, unexplained by subgroup analysis.

⁴ Downgraded by 1 increment if the confidence interval crossed one MID.

⁵Downgraded by 2 increments if the confidence interval crossed two MIDs.

Table 115: Clinical evidence profile: Guanfacine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guanfacine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (DSM-IV RS); 0-54; lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 8.1 lower (14.47 to 1.73 lower)	MODERATE	CRITICAL
ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 4.4 lower (7.55 to 1.25 lower)	MODERATE	CRITICAL
ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 3.7 lower (7.56 lower to 0.16 higher)	MODERATE	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

Table 116: Clinical evidence profile: Guanfacine versus dexamphetamine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guanfacine versus dexamphetamine	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (DSM-IV RS total scores); 0-54; lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 1.9 lower (8.81 lower to 5.01 higher)	MODERATE	CRITICAL

ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale); 0-27; lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	17	17	-	MD 1.2 lower (4.69 lower to 2.29 higher)	MODERATE	CRITICAL
ADHD hyperactivity symptoms investigator rated (DSM-IV RS Hyperactive subscale); 0-27; lower values are beneficial; 6 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	17	17	-	MD 0.7 lower (4.56 lower to 3.16 higher)	LOW	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

² Downgraded by 2 increments if the confidence interval crossed two MIDs.

Table 117: Clinical evidence profile: Reboxetine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reboxetine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (CAARS total scores); 0-54, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ³	none	22	17	-	MD 5.58 lower (11.18 lower to 0.02 higher)	LOW	CRITICAL
ADHD inattention symptoms investigator rated (CAARS Inattentive subscale); 0-27; lower values are beneficial; 6 weeks												
1	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	Serious ³	none	22	17	-	MD 4.74 lower (7.83 to 1.65 lower)	VERY LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated (CAARS Hyperactivity subscale); 0-27; lower values are beneficial; 6 weeks												
1	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	Serious ³	none	22	17	-	MD 0.93 lower (4.12 lower to 2.26 higher)	VERY LOW	CRITICAL
Behavioural outcomes (Global Assessment of Functioning); 0-100, higher values are beneficial; 6 weeks												
1	randomised	very	no serious	no serious	no serious	none	22	17	-	MD 1.08 lower (0.68	LOW	IMPORTANT

	trials	serious ²	inconsistency	indirectness	imprecision					to 1.48 lower)		
Discontinuation due to adverse events (follow-up 6 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	none	2/23 (8.7%)	1/17 (5.9%)	RR 1.48 (0.15 to 15)	28 more per 1000 (from 50 fewer to 824 more)	LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias.

² Downgraded by 2 increment if the majority of the evidence was at very high risk of bias.

³ Downgraded by 1 increment if the confidence interval crossed one MID.

⁴ Downgraded by 2 increments if the confidence interval crossed two MIDs.

Table 118: Clinical evidence profile: Venlafaxine versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Venlafaxine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms self rated (CAARS ADHD index); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	21	-	MD 13.3 lower (19.34 to 7.26 lower)	MODERATE	IMPORTANT
ADHD inattention symptoms self rated (CAARS Inattentive subscale); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	20	21	-	MD 8.7 lower (14.21 to 3.19 lower)	LOW	IMPORTANT
ADHD hyperactivity symptoms self rated (CAARS Hyperactive/Impulsive subscale); 0-27, lower values are beneficial; 6 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	21	-	MD 15.25 lower (22.19 to 8.31 lower)	MODERATE	IMPORTANT
Discontinuation due to adverse events (follow-up 6 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	1/22 (4.5%)	0/22 (0%)	OR 7.39 (0.15 to 372.38)	44 more per 1000 (from 71 fewer to 163 more)	VERY LOW	CRITICAL

Serious adverse events (follow-up 6 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	0/22 (0%)	0/22 (0%)	RD 0.00 (-0.08 to 0.08)	0 events in both arms	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 12 increments if the confidence interval crossed two MIDs.

Table 119: Clinical evidence profile: Bupropion versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SR Bupropion versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54 lower values are beneficial at 7 weeks; change scores reported												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	11	11	-	MD 1.3 lower (8.77 lower to 6.17 higher)	VERY LOW	CRITICAL
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54 lower values are beneficial at 6 weeks; final values reported												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	21	21	-	MD 10.72 lower (18.57 to 2.87 lower)	MODERATE	CRITICAL
CGI score of 1 or 2 (follow-up 7 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	7/11 (63.6%)	3/11 (27.3%)	RR 2.33 (0.81 to 6.76)	363 more per 1000 (from 52 fewer to 1000 more)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up 7 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	0/11 (0%)	1/11 (9.1%)	OR 0.14 (0 to 6.82)	77 fewer per 1000 (from 91 fewer to 315 more)	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 two MIDs.

Table 120: Clinical evidence profile: Bupropion versus methylphenidate

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SR Bupropion versus methylphenidate	Control	Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (ADHD-RS total scores); 0-54 lower values are beneficial at 7 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	11	8	-	MD 3.6 lower (10.65 lower to 3.45 higher)	LOW	CRITICAL
CGI score of 1 or 2 (follow-up 7 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	7/11 (63.6%)	4/8 (50%)	RR 1.27 (0.56 to 2.9)	135 more per 1000 (from 220 fewer to 950 more)	VERY LOW	CRITICAL
Discontinued due to adverse events (follow-up 7 weeks)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	0/11 (0%)	2/8 (25%)	OR 0.08 (0 to 1.45)	224 fewer per 1000 (from 250 fewer to 76 more)	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 two MIDs.

Table 121: Clinical evidence profile: Modafinil versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil versus placebo	Control	Relative (95% CI)	Absolute		
Quality of Life (follow-up 9 weeks; Better indicated by lower values); 9 weeks												

1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	142	51	-	MD 1.38 higher (1.35 lower to 4.11 higher)	LOW	CRITICAL
ADHD total symptoms (Adult ADHD self-report scores); 0-54, lower values are beneficial; 9 weeks												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	142	51	-	MD 3.73 lower (8.31 to 0.85 lower)	LOW	CRITICAL
ADHD total symptoms investigator rated (DSM IV RS total scores); 0-54, lower values are beneficial; 2 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	21	21	-	MD 10.5 lower (16.92 to 4.08 lower)	MODERATE	CRITICAL
ADHD inattention symptoms investigator rated (DSM-IV RS Inattentive subscale);0-27, lower values are beneficial; 2 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	21	-	MD 6.1 lower (9.02 to 3.18 lower)	HIGH	CRITICAL
ADHD hyperactivity symptoms investigator rated (DSM IV RS Hyperactive subscale); 0-27, lower values are beneficial; 2 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	21	21	-	MD 4.9 lower (8.89 to 0.91 lower)	MODERATE	CRITICAL
BRIEF-A (follow-up 9 weeks; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	141	51	-	MD 3.11 lower (7.25 to 1.03 higher)	LOW	CRITICAL
Discontinuation due to adverse events (follow-up 9 weeks)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/264 (26.1%)	6/74	RR 3.22 (1.46 to 7.13)	180 more per 1000 (from 110 more to 260 more)	LOW	CRITICAL

¹ Downgraded by 2 increment 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 122: Clinical evidence profile: Modafinil versus dexamphetamine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil versus dexamphetamine		Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (DSM-IV total scores); 0-54, lower values are beneficial; 7 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	21	21	-	MD 1.7 lower (8.5 lower to 5.1 higher)	MODERATE	CRITICAL
ADHD inattention symptoms investigator rated (DSM-IV Inattentive subscale); 0-27, lower values are beneficial, final values reported; 7 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	21	21	-	MD 0.5 lower (4.15 lower to 3.15 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated (DSM-IV Hyperactive subscale); 0-27, lower values are beneficial, final values reported; 7 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	21	21	-	MD 1.7 lower (5.28 lower to 1.88 higher)	MODERATE	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed one MID.

² Downgraded by 2 increments if the confidence interval crossed two MIDs.

Table 123: Clinical evidence profile: Atomoxetine and bupirone versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modafinil versus dexamphetamine		Relative (95% CI)	Absolute		
ADHD total symptoms investigator rated (AISRS total scores); 0-54; lower values are beneficial; 8 weeks												

1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious ¹	none	97	47	-	MD 4.8 lower (7.74 to 1.86 lower)	LOW	CRITICAL
ADHD inattention symptoms investigator rated inattention subscale (AISRS); 0-27; lower values beneficial; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	97	47	-	MD 1.6 lower (3.56 lower to 0.36 higher)	LOW	CRITICAL
ADHD hyperactivity symptoms investigator rated hyperactivity subscale (AISRS); 0-27; lower values beneficial; 8 weeks												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	97	47	-	MD 3.24 lower (5.63 to 0.85 lower)	LOW	CRITICAL
Discontinued due to adverse events												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	Serious ²	none	97	47	RR 1.04 (0.45 to 2.37)	6 more per 1000 (from 82 fewer to 204 more)	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.

F.2 Pharmacological sequencing

F.2.1 Pre-school children (under the age of 5)

No clinical evidence.

F.2.2 Children and young people (aged 5 to 18)

Table 124: Clinical evidence profile: Methylphenidate versus placebo 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	Methylphenidate versus placebo	Control	Relative (95% CI)	Absolute		
Discontinued treatment due to adverse events												

1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/9 (11.1%)	8.3%	RR 1.33 (0.1 to 18.57)	27 more per 1000 (from 75 fewer to 1000 more)	VERY LOW	CRITICAL
Serious adverse events												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/9 (0%)	0%	not pooled	not pooled	LOW	CRITICAL

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

² Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 125: Clinical evidence profile: Guanfacine AM versus placebo 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	Guanfacine AM versus placebo	Control	Relative (95% CI)	Absolute		
CGI-I improved or much improved or very much improved												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	110/148 (74.3%)	57.9%	RR 1.28 (1.09 to 1.51)	162 more per 1000 (from 52 more to 295 more)	VERY LOW	CRITICAL
Early discontinuation of treatment due to adverse events												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	4/150 (2.7%)	0.7%	RR 4.08 (0.46 to 36.08)	22 more per 1000 (from 4 fewer to 246 more)	VERY LOW	CRITICAL
Severe TEAs												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	very serious ³	none	3/150 (2%)	0.7%	RR 3.06 (0.32 to 29.09)	14 more per 1000 (from 5 fewer to 197 more)	VERY LOW	CRITICAL
ADHD-RS-IV inattention subscale: placebo adjusted LS mean reduction - New Subgroup (Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	150	153	-	SMD 0.36 lower (0.59 to 0.13 lower)	VERY LOW	CRITICAL

ADHD-RS-IV: placebo adjusted LS mean reduction (Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	150	153	-	SMD 0.337 lower (0.56 to 0.11 lower)	VERY LOW	CRITICAL
ADHD-RS-IV hyperactivity/impulsivity subscale: placebo adjusted LS mean reduction - New Subgroup (Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	150	153	-	SMD 0.36 lower (0.59 to 0.14 lower)	VERY LOW	CRITICAL

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

² The majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)

³ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 126: Clinical evidence profile: Guanfacine PM versus placebo 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	Guanfacine PM versus placebo	Control	Relative (95% CI)	Absolute		
CGI-I improved or much improved or very much improved												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	105/149 (70.5%)	57.9%	RR 1.22 (1.03 to 1.44)	127 more per 1000 (from 17 more to 255 more)	VERY LOW	CRITICAL
Early discontinuation of treatment due to adverse events												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	6/152 (3.9%)	0.7%	RR 6.04 (0.74 to 49.57)	35 more per 1000 (from 2 fewer to 340 more)	VERY LOW	CRITICAL
Severe TEAEs												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	10/152 (6.6%)	0.7%	RR 10.07 (1.3 to 77.67)	63 more per 1000 (from 2 more to 537 more)	VERY LOW	CRITICAL
ADHD-RS-IV inattention subscale: placebo adjusted LS mean reduction - New Subgroup (Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	152	153	-	SMD 0.46 lower (0.69 to 0.24 lower)	VERY LOW	CRITICAL

ADHD-RS-IV: placebo adjusted LS mean reduction - New Subgroup (Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	152	153	-	SMD 0.40 lower (0.62 to 0.17 lower)	VERY LOW	CRITICAL
ADHD-RS-IV hyperactivity/impulsivity subscale: placebo adjusted LS mean reduction - New Subgroup (Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	152	153	-	SMD 0.40 lower (0.62 to 0.17 lower)	VERY LOW	CRITICAL

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

² The majority of the evidence included an indirect population (downgrade by one increment) or a very indirect population (downgrade by two increments)

³ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 127: Clinical evidence profile: Risperidone versus placebo 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	Risperidone versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (parent rated ADHD-SC4, Severity Score, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	66	71	-	MD 0.20 lower (0.4 lower to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
ADHD total symptoms (teacher rated ADHD-SC4, Severity Score, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	none	38	48	-	MD 0.20 lower (0.43 lower to 0.03 higher)	⊕⊕OO LOW	CRITICAL
Inattention (parent rated ADHD-SC4 Severity, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	66	71	-	MD 0.20 lower (0.42 lower to 0.02 higher)	⊕⊕⊕O MODERATE	CRITICAL
Inattention (teacher rated ADHD-SC4 Severity, 0-3, high is poor) (Better indicated by lower values)												
1	randomised	serious ²	no serious	no serious	serious ¹	none	38	48	-	MD 0.20 lower (0.47	⊕⊕OO	CRITICAL

	trials		inconsistency	indirectness						lower to 0.07 higher)	LOW	
Hyperactivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	66	71	-	MD 0.20 lower (0.44 lower to 0.04 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Hyperactivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	none	38	48	-	MD 0.10 higher (0.14 lower to 0.34 higher)	⊕⊕○○ LOW	CRITICAL
Impulsivity (parent rated ADHD-SC4 Severity Subscore, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	66	71	-	MD 0.30 lower (0.57 to 0.03 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Impulsivity (teacher rated ADHD-SC4 Severity Subscore, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ¹	none	38	48	-	MD 0.20 lower (0.5 lower to 0.1 higher)	⊕⊕○○ LOW	CRITICAL
Function/behaviour (parent rated ODD DSM-IV, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	66	71	-	MD 0.30 lower (0.54 to 0.06 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Function/behaviour (teacher rated ODD DSM-IV, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	48	-	SMD 0 higher (0.26 lower to 0.26 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Function/behaviour (parent rated Peer Conflict Scale, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	66	71	-	MD 0.30 lower (0.49 to 0.11 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Function/behaviour (teacher rated Peer Conflict Scale, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	48	-	MD 0 higher (0.15 lower to 0.15 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Function/behaviour (parent rated CD DSM-IV, 0-3, high is poor) (Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	73	77	-	MD 0.10 lower (0.16 to 0.04 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Function/behaviour (teacher rated CD DSM-IV, 0-3, high is poor) (Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	very serious ¹	none	30	39	-	MD 0 higher (0.12 lower to 0.12 higher)	⊕○○○ VERY LOW	CRITICAL

¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

² 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 128: Clinical evidence profile: Lisdexamfetamine dimesylate versus placebo 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	Lisdexamfetamine dimesylate versus placebo	Control	Relative (95% CI)	Absolute		
Clinical response: >= 30% reduction in ADHD-RS-IV total score and CGI-I of 1 or 2												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	15/19 (78.9%)	42.9%	RR 1.84 (0.76 to 4.47)	360 more per 1000 (from 103 fewer to 1000 more)	VERY LOW	CRITICAL
Adverse events leading to hospitalisation/death/disability												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/19 (0%)	0%	not pooled	not pooled	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 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 129: Clinical evidence profile: Clonidine versus placebo 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	Clonidine versus placebo	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (ADHD-RS-IV improvement, high is poor) (Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	102	95	-	MD 4.20 lower (7.62 to 0.78 lower)	⊕○○○ VERY LOW	CRITICAL
Inattention (ADHD-RS-IV, high is poor) (Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	102	95	-	MD 2.00 lower (3.9 to 0.1 lower)	⊕○○○ VERY LOW	CRITICAL
Hyperactivity/impulsivity (ADHD-RS-IV, high is poor) (Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	102	95	-	MD 2.10 lower (3.92 to 0.28 lower)	⊕○○○ VERY LOW	CRITICAL
CGI-I (Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	102	95	-	MD 0.50 lower (0.84 to 0.16 lower)	⊕○○○ VERY LOW	CRITICAL
Discontinued treatment due to TEAE												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	1/102 (0.98%)	(3.1%)	RR 0.31 (0.03 to 2.96)	22 fewer per 1000 (from 30 fewer to 61 more)	⊕○○○ VERY LOW	CRITICAL

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

² Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 130: Clinical evidence profile: Lisdexamfetamine dimesylate versus atomoxetine for ADHD in children and young people

Quality assessment	No of patients	Effect	Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lisdexamfetamine dimesylate versus atomoxetine	Control	Relative (95% CI)	Absolute		
ADHD total symptoms (investigator rated ADHD-RS-IV, change score, 0-54, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	100	101	-	MD 6.90 lower (10.32 to 3.48 lower)	⊕⊕⊕⊕ MODERATE	CRITICAL
Hyperactivity/impulsivity (Investigator rated, ADHD-RS-IV, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	100	101	-	SMD 0.63 lower (0.91 to 0.35 lower)	⊕⊕⊕⊕ MODERATE	CRITICAL
Inattention (Investigator rated, ADHD-RS-IV, high is poor) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	100	101	-	SMD 0.62 lower (0.91 to 0.34 lower)	⊕⊕⊕⊕ MODERATE	CRITICAL
CGI improvement of at least one category												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	90/95 (94.7%)	(86.6%)	RR 1.09 (1 to 1.2)	78 more per 1000 (from 0 more to 173 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Discontinued treatment due to adverse event												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	8/128 (6.3%)	(7.5%)	RR 0.84 (0.34 to 2.05)	12 fewer per 1000 (from 49 fewer to 78 more)	⊕⊕⊕⊕ LOW	CRITICAL
Serious TEAE												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹	none	0/128 (0%)	(0%)	not pooled	not pooled	⊕⊕⊕⊕ LOW	CRITICAL
Function/behaviour (Parent rated, WFIRS-P, 0-3, high is poor) (Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	107	113	-	MD 0.08 lower (0.17 lower to 0.01 higher)	⊕⊕⊕○ MODERATE	CRITICAL
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¹ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

² Absolute effect calculated from risk difference

F.2.3 Adults

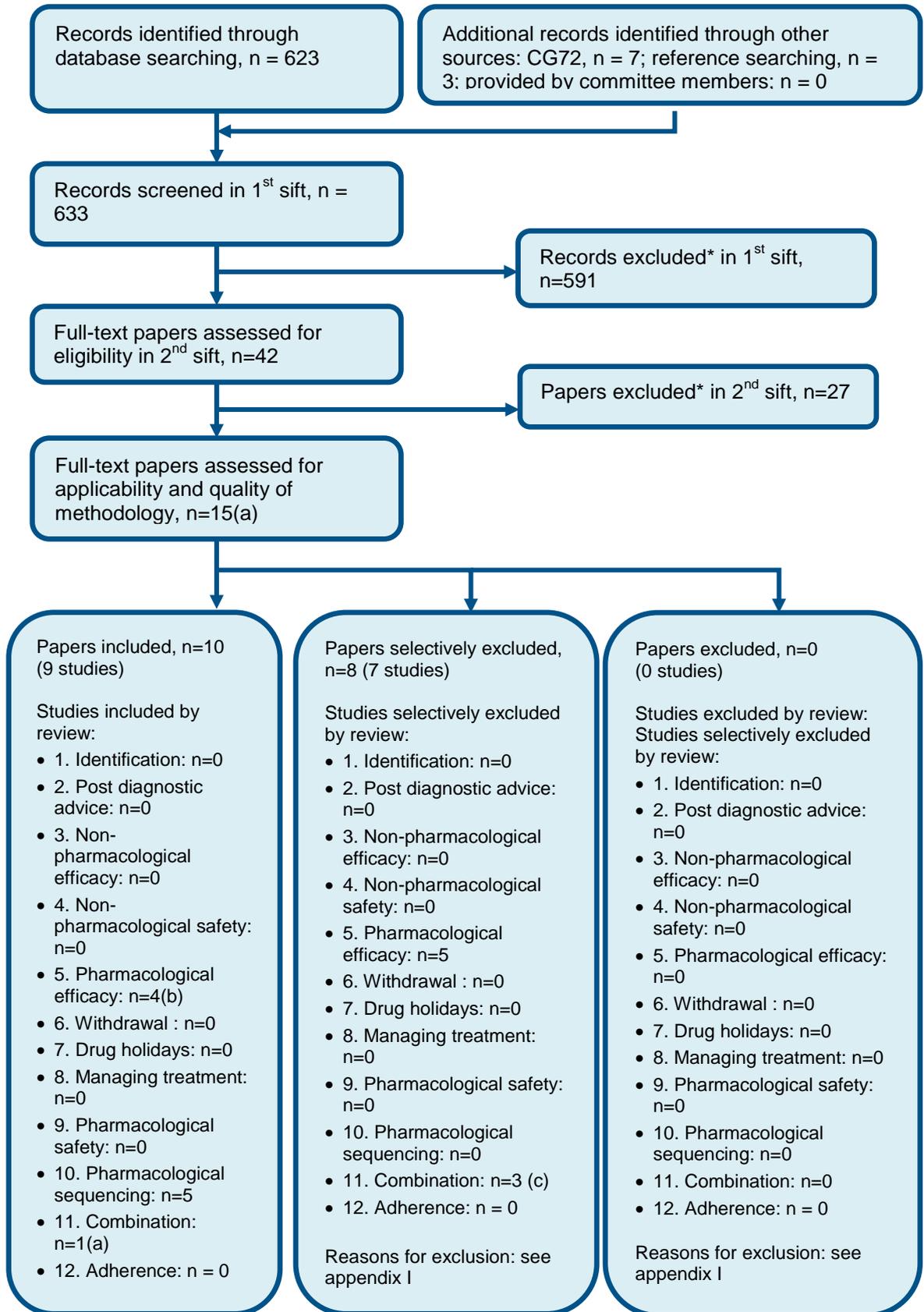
Table 131: Clinical evidence profile: Guanfacine versus placebo in adults with a sub-optimal response to CNS stimulants

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guanfacine	Placebo (while taking amphetamine treatment))	Relative (95% CI)	Absolute		
ADHD total symptoms (ADHD-RS, 0-54, high is poor) (measured with: Participants returned to study site for evaluation of ADHD symptoms; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness ²	very serious ³	none	13	13	-	MD 0.93 higher (5.44 lower to 7.3 higher)	⊕○○○ VERY LOW	CRITICAL
CGI-S (change score, 0-7) (measured with: Participants returned to study site for evaluation of ADHD symptoms; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness ²	very serious ³	none	13	13	-	MD 0.15 lower (0.75 lower to 0.45 higher)	⊕○○○ VERY LOW	CRITICAL
Adverse events leading to hospitalisation/death/disability												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness ²	no serious imprecision	none	0/13 (0%)	0/13 (0%)	not pooled	not pooled	⊕⊕○○ LOW	CRITICAL

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

² Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1 **Appendix G: Health economic evidence**
2 **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.

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2
3

Appendix H: Health economic evidence tables

H.1 Pharmacological efficacy

Study	[King 2006 ³⁷¹]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALY)</p> <p>Study design: Probabilistic decision analytic model</p> <p>Approach to analysis: Decision tree model as part of a Health Technology Assessment, with a 1 year time horizon in the base case. Considers alternative sequences of treatments that include 3 active treatments (a formulation of MPH, DEX, ATX followed by no treatment last) so in total 18 treatment strategies and a no treatment strategy. There were actually 38 strategies modelled with strategies featuring 1,2 or 3 active treatments</p>	<p>Population: Children aged 6 years</p> <p>Cohort settings: Start age: NR Male: NR</p> <p>Strategies include: 1. IR-MPH – ATX – DEX – NT 2. ER-MPH8 – ATX – DEX – NT 3. ER-MPH12 – ATX – DEX – NT 4. ATX – IR-MPH – DEX – NT 5. ATX – ER-MPH8 – DEX – NT 6. ATX – ER-MPH12 – DEX – NT 7. IR-MPH – DEX – ATX – NT 8. ER-MPH8 – DEX – ATX – NT 9. ER-MPH12 – DEX – ATX – NT</p>	<p>Total costs (mean per patient): 1. £1,233 2. £1,470 3. £1,479 4. £1,480 5. £1,550 6. £1,563 7. £1,140 8. £1,336 9. £1,410 10. £1,466 11. £1,485 12. £1,488 13. £1,098 14. £1,157 15. £1,159 16. £1,158 17. £1,177 18. £1,180 19. £1,223</p> <p>Currency & cost year: UK pounds 2003/4</p>	<p>QALYs (mean per patient): 1. 0.8279 2. 0.8273 3. 0.8278 4. 0.8278 5. 0.8277 6. 0.8274 7. 0.8283 8. 0.8277 9. 0.8284 10. 0.8281 11. 0.8281 12. 0.8278 13. 0.8289 14. 0.8287 15. 0.8287 16. 0.8288 17. 0.8288 18. 0.8285 19. 0.7727</p>	<p>ICER: Strategy 13 is dominant 95% CI: NR Probability Strategy 13 is cost-effective (£30K threshold): 31% when considering all 38 strategies, but 60% when comparing only the 19 strategies that have 3 active treatments per strategy.</p> <p>Also noted in the study that DEX is only licensed as a refractory treatment for children (not first line), and therefore strategies 13 to 18 may no longer be relevant, and therefore the optimal strategy then becomes 7.</p> <p>Analysis of uncertainty: States that a probabilistic analysis was undertaken (does not state the number of simulations used).</p> <p><u>Utility value sensitivity analysis:</u> Utility values were used which differentiated by the type of drug, so responders to ATX, IR-MPH (same utility used for DEX), and ER-MPH had</p>

<p>but 3 lines of treatment was found to be cost effective so only these strategies are the focus of the base case. Patients begin in titration on the first line treatment lasting 1 month. Patients only experience side effects and withdraw in the titration period, and move to the next treatment if they fail to respond during this period. Patients tolerating treatment will continue if they respond. Responders are assumed responsive for the rest of the year.</p> <p>Perspective: UK NHS Time horizon/Follow-up: 1 year Treatment effect duration:^(a) 1 year Discounting: Costs: NA ; Outcomes: NA</p>	<p>10. ATX – DEX – IR-MPH – NT 11. ATX – DEX – ER-MPH8 – NT 12. ATX – DEX – ER-MPH12 – NT 13. DEX – IR-MPH – ATX – NT 14. DEX – ER-MPH8 – ATX – NT 15. DEX – ER-MPH12 – ATX – NT 16. DEX – ATX – IR-MPH – NT 17. DEX – ATX – ER-MPH8 – NT 18. DEX – ATX – ER-MPH12 – NT 19. No Treatment</p>	<p>Cost components incorporated:</p> <ul style="list-style-type: none"> - Drug costs - Resource use associated with responders (psychiatrist, paediatrician, and GP consultations, and a blood test). - Resource use associated non responders (psychiatrist, paediatrician, and GP consultations, blood test, ECG, EEG, allergy test) 		<p>different utilities (with ATX being the highest), and a non responder utility to no medication was used for the non responders. The most cost effective intervention below the £20,000 threshold being intervention 10 (£15,448), but intervention 11 has an ICER just above the threshold of £20,173</p> <p><u>Co-morbid conditions sensitivity analysis:</u> Included additional healthcare resource use associated with comorbid conditions of CD and ODD. Strategy 13 remained dominant. If DEX is not suitable as a first line therapy then strategy 7 becomes optimal.</p> <p><u>Time horizon sensitivity analysis:</u> An extrapolation of the base case analysis extends the time horizon to when the cohort reaches age 18. A probability of remission is used over time (13% per year) for patients in all health states. Strategy 7 is the most cost effective.</p> <p><u>Resource use sensitivity analysis:</u> An alternative assumption is used that responders use more resource use than non-responders. Strategy 13 is optimal. Strategy 7 is optimal if DEX is not a suitable first line alternative.</p> <p><u>Sensitivity to structural assumption</u></p>
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			<p><u>regarding MPH:</u> The base case assumed that if a patient failed IR-MPH they would not receive another formulation of MPH. This sensitivity analysis considers a cohort of patients for whom a midday dose of medication is included unsuitable, including patients who failed IR-MPH or DEX because of non-response. Compares ER-MPH8, ER-MPH12, and ATX, and no treatment. ER-MPH12 is the most cost effective.</p> <p><u>Sensitivity to estimated response rates:</u> - Using all clinician rated response (CGI-S) – strategy 13 is optimal. If DEX is not used first line then strategy 7 is optimal. - Parent rated response synthesising all response rates (response rates estimated in extended MTC model: response defined on CGI-I, CGI-S, ADHD-RS or SNAP-IV) – strategy 13 is optimal. If DEX is not used first line then strategy 7 is optimal</p>
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Data sources

Health outcomes: The measure of clinical effectiveness is response rate to treatment, studies using the Clinical Global Impression Improvement subscale (CGI-I) are used in the base case analysis. 6 trials were included that met this criteria, and a mixed treatment comparison was used to bring this data together. 3 of these excluded subjects who were known non-responders to stimulant therapy. (This is contrary to the guideline effectiveness review where studies were excluded that specifically included only known responders or excluded known non responders. However this was not the case for all the studies used for the effectiveness of the King model and therefore as it is a mixed population it has been included). An important assumption in the model is that the treatment effects are independent of the treatments previously received.

Adverse events data: data was included from 10 trials that measured withdrawal rates. The withdrawal rates were calculated to include all reported withdrawal rates regardless of reason, which may overestimate the number of withdrawals from adverse events and sometimes lead to some double counting of non-responders. Withdrawal was also an outcome the mixed treatment comparison was used for.

Quality-of-life weights: In the base case analysis utility values used were from a poster presentation by Coghill 2004. EQ-5D. A mean of 0.837 for

responders, and 0.773 for non responders.

Cost sources: Resource use data was that used in a submission to this Health Technology Assessment (HTA) by Janssen-Cilag, who in turn got their data from a UK study on the management of ADHD in UK children. This data was updated with more up to date costs from NHS reference costs (2003). The average dose for each active medication was taken from the trials used in calculating response rates. Drug prices were obtained from published UK pricing lists (BNF), ER-MPH8 wasn't priced in the UK at the time and the price in the manufacturers' submission to the HTA was used.

Comments

Source of funding: HTA program

Limitations: Based on limited clinical data. Assumed independence of treatments in the sequence. Based on doses from the trials which may not represent doses in practice.

Other: Discounting in secondary extrapolation analysis was 6% for costs and 1.5% for benefits.

Overall applicability: partially applicable^(b) **Overall quality:** potentially serious^(c)

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; ATX: Atomoxetine; IR-MPH: immediate release methylphenidate; ER-MPH8: extended release methylphenidate with duration of action of 8 hours; ER-MPH12: extended release methylphenidate with duration of action of 12 hours; DEX: dexamphetamine; NT: No treatment; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; CD: Conduct disorder; ODD: Oppositional defiant disorder; MTC: Mixed Treatment Comparison; CGI-S: Clinical Global Impression Severity subscale; ADAD-RS: ADHD Rating Scale; SNAP-IV: Swanson, Nolan, and Pelham, Version IV Scale for ADHD.

(a) It is not stated how long the trials were from that the model is based on, however the study says 'it was deemed inappropriate to extend the time horizon beyond the time frame covered by the available clinical data'. For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable/Partially applicable/Not applicable

(c) Minor limitations/Potentially serious limitations / Very serious limitations

Study	[Cottrell 2008 ¹⁸⁸]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALY)</p> <p>Study design: Probabilistic decision analytic model</p> <p>Approach to analysis:</p>	<p>Population: Children with ADHD</p> <p>Subgroup 1: Stimulant naïve patients with no history of pharmacotherapy use and no contraindications to stimulants.</p> <p>Subgroup 2: stimulant-</p>	<p>Total costs (mean per patient):</p> <p>Subgroup 1 (a): Strategy 1: £125.76 Strategy 2: £534.09 Incremental (2-1): £408.34 (95% CI: NR; p=NR)</p>	<p>QALYs (mean per patient):</p> <p>Subgroup 1 (a): Strategy 1: 0.9040 Strategy 2: 0.9308 Incremental (2-1): 0.0268 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1):</p> <p>Subgroup 1 (a): £15,224 per QALY gained (pa) 95% CI: NR Probability strategy 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 1 (b):</p>

<p>Markov model of 1 year with monthly cycles. Compares treatment algorithms that include atomoxetine with current treatment algorithms. Consists of 18 states; 4 per treatment for the active treatments based on the combinations of whether a patient responds and if they have adverse events, and 2 states for no treatment based only on response or not. Treatment effects for response, adverse events, and relapse derived from various trials and pooled data. 5 subgroups were analysed but 2 met the criteria for this question of no previous medication.</p> <p>Perspective: UK NHS</p> <p>Time horizon/Follow-up: 1 year</p> <p>Treatment effect duration:^(a) 1 year</p> <p>Discounting: Costs: NA ; Outcomes: NA</p>	<p>contraindicated patients (naïve) with no history of pharmacotherapy use but are precluded from using stimulants for because of pre-existing conditions.</p> <p>Cohort settings: Start age: NR Male: NR</p> <p>Subgroup 1 (a): Strategy 1: IR-MPH →IR-DEX→no treatment Strategy 2: Atomoxetine →IR-MPH→IR-DEX →no treatment</p> <p>Subgroup 1 (b): Strategy 1: XR-MPH→IR-DEX→no treatment Strategy 2: Atomoxetine→XR-MPH→IR-DEX→no treatment</p> <p>Subgroup 2: Strategy 1: No treatment Strategy 2: Atomoxetine→ no treatment</p>	<p>Subgroup 1 (b): Strategy 1: £334.07 Strategy 2: £599.78 Incremental (2-1): £265.71 (95% CI: NR; p=NR)</p> <p>Subgroup 2: Strategy 1: £0 Strategy 2: £480.94 Incremental (2-1): £480.94 (95% CI: NR; p=NR)</p> <p>Currency & cost year: 2004 UK pounds</p> <p>Cost components incorporated: Only study drug costs are included.</p>	<p>Subgroup 1 (b): Strategy 1: 0.9140 Strategy 2: 0.9341 Incremental (2-1): 0.0201 (95% CI: NR; p=NR)</p> <p>Subgroup 2: Strategy 1: 0.8800 Strategy 2: 0.9217 Incremental (2-1): 0.0417 (95% CI: NR; p=NR)</p>	<p>£13,241 per QALY gained (pa) 95% CI: NR Probability strategy 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 2: £11,523 per QALY gained (pa) 95% CI: NR Probability strategy 2 cost-effective (£20K/30K threshold): NR</p> <p>Analysis of uncertainty: Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.</p> <p>A range of sensitivity analyses were performed (results not reported in paper and assumed these are deterministic) which showed that the utility values are important determinants of the cost effectiveness of atomoxetine. Additional sensitivity analyses on utilities were explored to see how the results of the model are affected when the differences between utility values of the different treatment for each health state were reduced. This was explored in stimulant naïve patients (subgroup 1). - When differences in the utility values between corresponding health states were reduced to 75% of the value given in the base case, the range of the ICER increased.</p>
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- When the difference was decreased to 25%, the ICER reached a range of £42,000-£62,000.

Data sources

Health outcomes: Treatment effects from the stimulant naïve group are based on a meta-regression of response data from randomised active comparator trials of atomoxetine and methylphenidate (some of these are open label or have been excluded from the clinical review because participants had previously received medication). It is not clear how response has been defined in this analysis. Assumption of parity between stimulants is assumed based on head to head trials of IR-MPH and XR-MPH. Relapse data derived from relapse prevention studies (for all subgroups).

Treatment effects for the stimulant contraindicated (naïve) group are based on responder rates from a randomised placebo-controlled trial of atomoxetine in patients with tics or Tourette's syndrome.

Adverse events data: the probability of 'one or more medication related adverse events' were pooled from the safety data of six randomised placebo controlled trials. Assumed parity between all treatments. It is assumed that 'the probability that a medication related adverse event is insomnia' is zero for atomoxetine. Probabilities of discontinuation are assumed the same regardless of treatment. (either from adverse events or lack of efficacy).

Quality-of-life weights: Utility values were from a study that surveyed 83 parents of children with ADHD in the UK using health state descriptions and standard gamble methodology.⁵⁶¹ It had states describing children treated with stimulants and non-stimulants, and also distinguished between immediate release and extended release methylphenidate. The health state corresponding to 'responder without side effects' for atomoxetine was assigned the highest utility (0.959). Health states corresponding to 'responder without side effects' for XR-MPH and IR-MPH had utility value of 0.930 and 0.913 respectively. Other states in the model that used utilities from the paper are 'responder with side effects', 'non-responder without side effects', 'non-responder with side effects', for the 3 treatments. For IR-DEX, parity with IR-MPH has been assumed. For the 'no medication' states, the utility from the child's own health state for the unmedicated patients (0.88) was used.

Cost sources: MIMS was used as the source of drug cost (June 2004). Calculation of the daily costs of the stimulants is based on average daily doses taken by patients (source cannot be found online – potentially data from a trial by Eli Lilly)

Comments

Source of funding: Financial support provided by Eli Lilly. Four of the eight authors work for the sponsor.

Limitations: Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.

Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. No adverse event costs or other resource use costs included. Potential conflict of interest

Other:

Overall applicability: partially applicable^(b) Overall quality: potentially serious/very serious limitations^(c)

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(d) It is not stated how long the trials were from that the model is based on, however the study says 'it was deemed inappropriate to extend the time horizon beyond the time frame covered by the available clinical data'. For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(e) Directly applicable/Partially applicable/Not applicable

(f) *Minor limitations/Potentially serious limitations / Very serious limitations*

Study	[Hong 2009 ³³¹]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALY)</p> <p>Study design: Probabilistic decision analytic model</p> <p>Approach to analysis: 1 year markov model with monthly cycles. 3 subgroup populations were included, but only 2 had no history of pharmacotherapy use and are included in this question. The model has 14 health states for the stimulant naïve group and 6 health states for the stimulant contraindicated group. For the stimulant naïve subgroup, an algorithm of atomoxetine first line followed by methylphenidate then no treatment is compared to methylphenidate first then atomoxetine then no treatment. For the</p>	<p>Population: Children with ADHD</p> <p>Subgroup 1: Stimulant naïve patients with no history of pharmacotherapy use and no contraindications to stimulants.</p> <p>Subgroup 2: stimulant-naïve patients with contraindications to stimulants with no history of pharmacotherapy use but are precluded from using stimulants for because of pre-existing conditions.</p> <p>Cohort settings: Start age: NR Male: NR</p> <p>Subgroup 1 (a) Strategy 1: IR-MPH→Atomoxetine→no treatment</p>	<p>Total costs (mean per patient):</p> <p>Subgroup 1 (a): Strategy 1: £331 Strategy 2: £946 Incremental (2-1): £615 (95% CI: NR; p=NR)</p> <p>Subgroup 1 (b): Strategy 1: £815 Strategy 2: £1,092 Incremental (2-1): £277 (95% CI: NR; p=NR)</p> <p>Subgroup 2: Strategy 1: £0 Strategy 2: £876 Incremental (2-1): £876 (95% CI: NR; p=NR)</p> <p>Currency & cost year: [2008 Spanish Euros reported here as 2008 UK pounds^(b)]</p> <p>Cost components incorporated: Only the pharmaceutical</p>	<p>QALYs (mean per patient):</p> <p>Subgroup 1 (a): Strategy 1: 0.910 Strategy 2: 0.930 Incremental (2-1): 0.02 (95% CI: NR; p=NR)</p> <p>Subgroup 1 (b): Strategy 1: 0.920 Strategy 2: 0.933 Incremental (2-1): 0.013 (95% CI: NR; p=NR)</p> <p>Subgroup 2: Strategy 1: 0.880 Strategy 2: 0.922 Incremental (2-1): 0.042 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1):</p> <p>Subgroup 1 (a): £31,007 per QALY gained (pa) 95% CI: NR Probability strategy 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 1 (b): £21,971 per QALY gained (pa) 95% CI: NR Probability strategy 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 2: £21,079 per QALY gained (pa) 95% CI: NR Probability strategy 2 cost-effective (£20K/30K threshold): NR</p> <p>Analysis of uncertainty: Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.</p> <p>A range of sensitivity analyses were</p>

<p>contraindicated group there are no stimulants in the algorithm.</p> <p>Perspective: Spanish national health service Time horizon/Follow-up: 1 year Treatment effect duration:^(a) 1 year Discounting: Costs: NA ; Outcomes: NA</p>	<p>Strategy 2: Atomoxetine→IR- MPH→no treatment</p> <p>Subgroup 1 (b) Strategy 1: XR- MPH→Atomoxetine→no treatment Strategy 2: Atomoxetine→XR- MPH→no treatment</p> <p>Subgroup 2: Strategy 1: No treatment Strategy 2: Atomoxetine</p>	<p>cost of treatment was included</p>		<p>performed (results not reported in paper and assumed these are deterministic) which showed that the utility values are important determinants of the cost effectiveness of atomoxetine. Additional sensitivity analyses on utilities were explored to see how the results of the model are affected when the differences between utility values of the different treatment for each health state were reduced. This was explored in stimulant naïve patients (subgroup 1). The smaller the differences in utilities between the treatments then the higher the ICER.</p>
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Data sources

Health outcomes: The transition probabilities reflecting the treatment effects of the model were the same as those from the Cottrell paper. It is not clear how response has been defined in this analysis. The adverse events were also from the same sources as the Cottrell paper. Parity sometimes assumed between IR-MPH and XR-MPH.

Quality-of-life weights: The utilities are also the same as those used in the Cottrell paper.⁵⁶¹

Cost sources: unit costs of the drugs were derived from the General Spanish Council of Pharmacists. Resource use on the average dose a day of stimulants was from 'market research'.

Comments

Source of funding: the study was sponsored by Eli Lilly

Limitations: Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.
Potential conflict of interest. Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. No adverse event costs or other resource use costs included. Could the assumed independence of drugs regardless of line of therapy alter the results?

Other: The model in this paper is an update of the model from the Cottrell paper. However the interventions are not the same (switching medications and not just atomoxetine vs sequence with no atomoxetine), there are less subgroups being considered also, therefore it was more appropriate to report it as a separate study.

Overall applicability: Partially applicable^(c) Overall quality: potentially serious/very serious limitations^(d)

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

- a) It is not stated how long the trials were from that the model is based on, however the study says 'it was deemed inappropriate to extend the time horizon beyond the time frame covered by the available clinical data'. For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
- b) Converted using 2008 purchasing power parities⁴⁸⁶. The cost year is not mentioned in the paper and so 2008 was assumed based on when the paper was submitted for publication.
- c) Directly applicable / Partially applicable / Not applicable
- d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[Zimovetz 2016 ⁷¹⁴]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALYs)</p> <p>Study design: Decision analytic model</p> <p>Approach to analysis: Decision tree model with a 1 year time horizon comparing lisdexamfetamine with ER methylphenidate and atomoxetine in adults. People can either tolerate or not tolerate the drug and then those who tolerate are responders or non-</p>	<p>Population: Adults with ADHD</p> <p>Cohort settings: Start age: NR Male: NR</p> <p>Intervention 1: Methylphenidate ER (MPH-ER)</p> <p>Intervention 2: Atomoxetine (ATX)</p> <p>Intervention 3: Lisdexamfetamine (LDX)</p> <p>(average doses not specified and taken from</p>	<p>Total costs (mean per patient): Intervention 1: £3387 Intervention 2: £3573 Intervention 3: £3378*</p> <p>Incremental (3-1): - £9 (95% CI: NR; p=NR) Incremental (3-2): - £195 (95% CI: NR; p=NR)</p> <p>Currency & cost year: 2015 UK pounds</p> <p>Cost components incorporated: Drug costs, other healthcare resource use such as; appointments</p>	<p>QALYs (mean per patient): Intervention 1: 0.718 Intervention 2: 0.714 Intervention 3: 0.724*</p> <p>Incremental (3-1): 0.005 (95% CI: NR; p=NR) Incremental (3-2): 0.009 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 3 versus Intervention 1): Intervention 3 dominant (pa) 95% CI: NR Probability Intervention 3 cost-effective (£20K): 61%</p> <p>ICER (Intervention 3 versus Intervention 2): Intervention 3 dominant (pa) 95% CI: NR Probability Intervention 3 cost-effective (£20K): 80%</p> <p>Analysis of uncertainty: For the PSA 5000 simulations were performed.</p> <p>Additional sensitivity analyses were conducted on the following parameters;</p> <ul style="list-style-type: none"> Efficacy; taking the upper and lower intervals of the relative risks of effect. Discontinuation rates; upper and lower bounds based on +/- 1 SD.

<p>responders. An NMA informs treatment effect and discontinuation risks. Costs also include resource use associated with response and non-response.</p> <p>Perspective: UK NHS Time horizon/Follow-up: 1 year Treatment effect duration:^(a) 1 year Discounting: Costs: NA ; Outcomes: NA</p>	<p>a weighted average of the NMA informing the treatment effect)</p>	<p>with clinicians (psychiatrists, psychologists, nurses, GP's), measuring blood pressure and weight and having ECG, EEG and allergy test.</p> <p>*Note that these are the probabilistic results, and as LDX vs MPH-ER and LDX vs ATX was run as two separate analyses the cost and QALY for LDX is the average of the LDX arm in each analysis.</p>		<ul style="list-style-type: none"> • Utilities; a different source was used which had a higher response utility but the same non-response utility. • Resource use; cost of responders increased by one more visit to a GP and psychiatrist. • Time horizon; extended to 5 years with all assumptions the same • Drug costing; applied drug costs to 'real world drug utilisation' from IMS. • Length of titration period; length of titration for ATX extended to 84 days <p>In the MPH-ER comparison, results were sensitive to the discontinuation rates (when these were at the lower bound LDX had an ICER of £43,525). LDX was also sensitive to resource use and drug costs assumptions but was still cost effective. LDX was still dominant vs ATX in all sensitivity analyses.</p> <p>Scenario analyses;</p> <ul style="list-style-type: none"> • Time horizon extended to 5 years and non-responder annual resource adjusted to reflect lower frequency of follow up expected in the longer term based on possible decline over time of ADHD symptoms (decreased by one visit to psychologist and GP). This was once with base case utilities and once with SA utilities. This scenario with the base case utilities meant LDX was no longer dominant against MPH-ER (ICER: £477), similar for when the SA utilities were used. LDX vs ATX was still dominant. • Patients who discontinue are assumed to have same utility during titration period as responders and then the same as non-responders.
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Results were very similar to the base case.

- An analysis comparing LDX to MPH-IR, assuming same efficacy and titration dose as MPH-ER but different cost and maintenance dose.

ICER of LDX vs MPH-IR: £19,362.

Data sources

Health outcomes: Treatment effect derived from an NMA. This included studies that had outcomes of CGI-I, ADHD-RS IV, and discontinuation. ADHD-RS-IV scores were imputed onto CGI-I using quadratic regression for ATX studies as these had no CGI-I outcomes. Overall 21 studies were included in the NMA. Not clear which ones for which outcomes (as some are just used in sensitivity analyses), but 10 of the 21 are included in the guideline pharmacological effectiveness review, and therefore if not all are used in the core analysis then it is likely a higher proportion are also included in the guideline review. Relative risks reported from the NMA are 2.14 for LDX, 1.65 for ATX, and 1.84 for MPH-ER. Relative risks for discontinuation are 3.21 for LDX, 2.67 for ATX, and 2.76 for MPH-ER. The average mean final dose calculated in LDX arms ranged from 51.38 mg/day to 51.50 mg/day. The average dose for ATX ranged from 80.00 mg/day to 87.67 mg/day. The average dose for MPH-ER ranged from 36.88 mg/day to 58.95 mg/day. These average doses were consistent with the recommended doses of these drugs for adults.

Patients begin titration which lasts 28 days. Patients who experience intolerable side effects discontinue treatment in the middle of the titration period and remain on no treatment for the rest of the model. For these patients utilities and costs during the titration period are represented by a 50/50 mix of the responder and non-responder utility values and non-drug costs. Non responder costs and utilities are applied for the rest of the model. (The paper states that 'those who discontinue, the same as non-responders are assumed to receive behavioural therapy' – this isn't actually something that is in the model). At the end of the titration period, non-responding patients discontinue treatment and are assigned the costs and utilities of a non-responder for the titration period and the whole model time horizon. Patients who respond to treatment at the end of the titration period remain on treatment and responding for the rest of the model.

Quality-of-life weights: EQ-5D UK tariff, collected using a web based survey by Mitsi 2010. Utilities of 0.76 for responders and 0.68 for non-responders.

Cost sources: Resource use of healthcare resources for responders and non-responders is derived from a survey the authors undertook with 60 psychiatrists (survey reported in supplementary material). However it is not clear how the answers to these questions are being translated into the resource use reported in table 3 in the paper. Non-drug costs translated to £115.84 per month for a responder and £337.82 for each non-responder. Cost sources are the PSSRU 2015 (and 2013 for psychologist but inflated to 2015 in the paper), NHS reference costs 2014-15, and the BNF.

Comments

Source of funding: Funded by Shire (manufacturer of Elvanse – a brand of LDX) **Limitations:** Are interventions appropriate for an adult population compared in the same line of treatment? Potential conflict of interest. No additional treatment assumed following non response/discontinuation. NMA methods a combination of dichotomous outcomes and continuous transformed to dichotomous. Some studies in their NMA we haven't included in our review. Methods sometimes unclear; resource use estimates. No adverse event costs included. **Other:**

Overall applicability: Directly applicable^(b) **Overall quality:** Potentially serious limitations^(c)

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years

- a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
- b) Directly applicable / Partially applicable / Not applicable
- c) Minor limitations / Potentially serious limitations / Very serious limitations

H.2 Pharmacological sequencing

Study	[Cottrell 2008 ¹⁸⁸]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALY)</p> <p>Study design: Probabilistic decision analytic model</p> <p>Approach to analysis: Markov model of 1 year with monthly cycles. Compares treatment algorithms that include atomoxetine with current treatment algorithms. Consists of 18 states; 4 per treatment for the active treatments based on the combinations of whether a patient responds and if they have adverse events, and 2 states for no treatment based only on response or not. Treatment effects for response, adverse</p>	<p>Population: Children with ADHD Subgroup 1: Stimulant failed patients; previously used methylphenidate but it was intolerable or ineffective. Subgroup 2: stimulant-averse (exposed) patients; have responded successfully to stimulants but would like to stop if other medication was available. Subgroup 3: stimulant contraindicated (exposed) patients; have previously been treated with stimulants but are now precluded from using them.</p> <p>Cohort settings: Start age: NR Male: NR</p>	<p>Total costs (mean per patient): Subgroup 1: Intervention 1: £39.48 Intervention 2: £488.26 Incremental (2-1): £448.78 (95% CI: NR; p=NR)</p> <p>Subgroup 2 (a): Intervention 1: £119.27 Intervention 2: £493.05 Incremental (2-1): £373.79 (95% CI: NR; p=NR)</p> <p>Subgroup 2 (b): Intervention 1: £312.23 Intervention 2: £568.96 Incremental (2-1): £256.3 (95% CI: NR; p=NR)</p> <p>Subgroup 3: Intervention 1: £0</p>	<p>QALYs (mean per patient): Subgroup 1: Intervention 1: 0.8967 Intervention 2: 0.9268 Incremental (2-1): 0.03 (95% CI: NR; p=NR)</p> <p>Subgroup 2 (a): Intervention 1: 0.9028 Intervention 2: 0.9263 Incremental (2-1): 0.0235 (95% CI: NR; p=NR)</p> <p>Subgroup 2 (b): Intervention 1: 0.9120 Intervention 2: 0.9301 Incremental (2-1): 0.0181 (95% CI: NR; p=NR)</p> <p>Subgroup 3: Intervention 1: 0.88 Intervention 2: 0.9120</p>	<p>ICER (Intervention 2 versus Intervention 1): Subgroup 1: £14,945 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 2 (a): £15,878 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 2 (b): £14,169 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR</p> <p>Subgroup 3: £12,370 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR</p>

Study		[Cottrell 2008 ¹⁸⁸]		
<p>events, and relapse derived from various trials and pooled data. 5 subgroups were analysed but 3 met the criteria for this question of failing, being averse, or contraindicated to certain medications.</p> <p>Perspective: UK NHS</p> <p>Time horizon/Follow-up: 1 year</p> <p>Treatment effect duration:^(a) 1 year</p> <p>Discounting: Costs: NA ; Outcomes: NA</p>	<p>Subgroup 1: Intervention 1: IR-DEX→no treatment Intervention 2: Atomoxetine →IR-DEX →no treatment</p> <p>Subgroup 2 (a): Intervention 1: IR-MPH→IR-DEX→no treatment Intervention 2: Atomoxetine→IR-MPH→IR-DEX→no treatment</p> <p>Subgroup 2 (b): Intervention 1: XR-MPH→IR-DEX→no treatment Intervention 2: Atomoxetine→XR-MPH→IR-DEX→no treatment</p> <p>Subgroup 3: Intervention 1: No treatment Intervention 2: Atomoxetine→ no treatment</p>	<p>Intervention 2: £395.98 Incremental (2-1): £395.98 (95% CI: NR; p=NR)</p> <p>Currency & cost year: 2004 UK pounds</p> <p>Cost components incorporated: Only study drug costs are included.</p>	<p>Incremental (2-1): 0.0320 (95% CI: NR; p=NR)</p>	<p>Analysis of uncertainty: Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.</p> <p>A range of sensitivity analyses were performed (results not reported in paper and assumed these are deterministic) which showed that the utility values are important determinants of the cost effectiveness of atomoxetine.</p>

Data sources

Health outcomes: Treatment effects from the stimulant failed group (not contraindicated i.e. Subgroup 1 above) are based on responder rates in a crossover trial of IR-MPH and IR-DEX (Efron 1997) (It is assumed that this response probability being used would be that of proportion of people who

Study	[Cottrell 2008 ¹⁸⁸]
<p>failed on MPH but then responded to DEX). Parity is assumed for atomoxetine and DEX for those who failed MPH. Probability of response for no medication is derived from factoring down the rate of DEX responders in MPH failed patients by applying the relative risk of response for placebo vs ATX for stimulant naïve patients derived from the meta-regression analysis (that was used for the treatment effect in the stimulant naïve patients – which was a subgroup of this paper presented in the general pharmacological effectiveness review).</p> <p>Treatment effect for the stimulant averse (exposed) patients were based on a meta-regression analysis. The meta-regression analysis sub-grouped patients by patient stimulant history so the response rates for the stimulant exposed group is used here. Assumptions of parity are used between MPH types. Parity is also assumed for ATX and DEX as above. No medication response is the same as for the above subgroup. Treatment effects for the stimulant contraindicated (exposed) group are based on responder rates from a randomised placebo-controlled trial of atomoxetine in patients with tics or Tourette’s syndrome.</p> <p>Adverse events data: the probability of ‘one or more medication related adverse events’ were pooled from the safety data of six randomised placebo controlled trials. Assumed parity between all treatments. It is assumed that ‘the probability that a medication related adverse event is insomnia’ is zero for atomoxetine. Probabilities of discontinuation are assumed the same regardless of treatment. (either from adverse events or lack of efficacy).</p> <p>Quality-of-life weights: Utility values were from a study that surveyed 83 parents of children with ADHD in the UK using health state descriptions and standard gamble methodology⁵⁶¹. It had states describing children treated with stimulants and non-stimulants, and also distinguished between immediate release and extended release methylphenidate. The health state corresponding to ‘responder without side effects’ for atomoxetine was assigned the highest utility (0.959). Health states corresponding to ‘responder without side effects’ for XR-MPH and IR-MPH had utility value of 0.930 and 0.913 respectively. Other states in the model that used utilities from the paper are ‘responder with side effects’, ‘non-responder without side effects’, ‘non-responder with side effects’, for the 3 treatments. For IR-DEX, parity with IR-MPH has been assumed. For the ‘no medication’ states, the utility from the child’s own health state for the unmedicated patients (0.88) was used.</p> <p>Cost sources: MIMS was used as the source of drug cost (June 2004). Calculation of the daily costs of the stimulants is based on average daily doses taken by patients (source cannot be found online – potentially data from a trial by Eli Lilly)</p>	

Comments
<p>Source of funding: Financial support provided by Eli Lilly. Four of the eight authors work for the sponsor. Limitations: Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public.</p> <p>Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. No adverse event costs or other resource use costs included. Potential conflict of interest. Other:</p> <p>Overall applicability: partially applicable^(b) Overall quality: potentially serious limitations^(c)</p>

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(g) It is not stated how long the trials were from that the model is based on, however the study says ‘it was deemed inappropriate to extend the time horizon beyond the time frame covered by the available clinical data’. For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(h) Directly applicable / Partially applicable / Not applicable

(i) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[Hong 2009 ³³¹]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALY)</p> <p>Study design: Probabilistic decision analytic model</p> <p>Approach to analysis: 1 year markov model with monthly cycles. 3 subgroup populations were included, but only 1 had previously tried stimulant and is included in this question. The model has 6 health states for the stimulant failed group.</p> <p>Perspective: Spanish national health service</p> <p>Time horizon/Follow-up: 1 year</p> <p>Treatment effect duration:^(a) 1 year</p> <p>Discounting: Costs: NA ; Outcomes: NA</p>	<p>Population: Children with ADHD</p> <p>The study has 3 subgroups but only one fits into this question as having a population that have previously tried stimulants and failed due to lack of efficacy or intolerable side effects (the other 2 have been included in the other pharmacological effectiveness review).</p> <p>Cohort settings: Start age: NR Male: NR</p> <p>Intervention 1: No treatment</p> <p>Intervention 2: Atomoxetine</p>	<p>Total costs (mean per patient): Intervention 1: £0 Intervention 2: £831 Incremental (2-1): £831 (95% CI: NR; p=NR)</p> <p>Currency & cost year: [2008 Spanish Euros reported here as 2008 UK pounds^(b)]</p> <p>Cost components incorporated: Only the pharmaceutical cost of treatment was included</p>	<p>QALYs (mean per patient): Intervention 1: 0.880 Intervention 2: 0.919 Incremental (2-1): 0.039 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1): £21,528 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR</p> <p>Analysis of uncertainty: Probabilistic sensitivity analysis stated as being done with 20,000 simulations. However it is unclear if the base case results are probabilistic.</p> <p>A range of sensitivity analyses were performed (results not reported in paper and assumed these are deterministic) which showed that the utility values are important determinants of the cost effectiveness of atomoxetine.</p>
Data sources				
<p>Health outcomes: The transition probabilities reflecting the treatment effects for the stimulant failed group were derived from responder rates in patients treated with ATX after a failure of an initial 6 week treatment with XR-MPH in a randomised crossover study of MPH and ATX (Newcorn 2008⁴⁷⁵). A probability of response on no medication in this population was derived by applying the relative risk of response for placebo versus ATX drawn from a meta-regression analysis (Bae 2004).</p>				

Study	[Hong 2009³³¹]
<p>Quality-of-life weights: The utilities are also the same as those used in the Cottrell paper.</p> <p>Cost sources: unit costs of the drugs were derived from the General Spanish Council of Pharmacists. Resource use on the average dose a day of stimulants was from 'market research'.</p>	
Comments	
<p>Source of funding: the study was sponsored by Eli Lilly. Limitations: non UK. Population quite vague. Does not use EQ-5D and valuations of the states are based on parents not the general public. Potential conflict of interest. Methods sometimes unclear; including if results are probabilistic, if transition probabilities from trials have been extrapolated. Assumptions made about parity where there is no data. No adverse event costs or other resource use costs included. Treatment effect source not included in clinical review – was excluded because it excluded patients who had previously not responded to the treatments. This may lead to an overestimation of the treatment effect of patients recruited in a trial if they have a history of responding, but there were also drug naïve patients included in the trial and as it was not the entire trial population that were previous responders a judgement was made to include this economic evaluation. Other: The model in this paper is an update of the model from the Cottrell paper. However the interventions are not the same (switching medications and not just atomoxetine vs sequence with no atomoxetine), there are less subgroups being considered also, therefore it was more appropriate to report it as a separate study.</p>	
<p>Overall applicability: Partially applicable^(c) Overall quality: potentially serious limitations^(d)</p>	

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IR-MPH: immediate release methylphenidate, EX-MPH: extended release methylphenidate, IR-DEX: immediate release dexamphetamine NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

- e) It is not stated how long the trials were from that the model is based on, however the study says 'it was deemed inappropriate to extend the time horizon beyond the time frame covered by the available clinical data'. For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
- f) Converted using 2008 purchasing power parities.⁴⁸⁶ The cost year is not mentioned in the paper and so 2008 was assumed based on when the paper was submitted for publication.
- g) Directly applicable / Partially applicable / Not applicable
- h) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[Faber 2008²²¹]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALYs)</p> <p>Study design: deterministic decision analytic model</p> <p>Approach to analysis:</p>	<p>Population: In primary phase: Children and young people who show sub optimal symptom control with IR MPH (assumed 42% of youths starting</p>	<p>Total costs (mean per patient): Intervention 1: £7,095 Intervention 2: £8,416 Incremental (2-1): £1,321</p>	<p>QALYs (mean per patient): Intervention 1: 7.66 Intervention 2: 7.79 Incremental (2-1): 0.13 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1): £10,161 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR</p>

Study	[Faber 2008 ²²¹]			
<p>Markov model with a 10 year time horizon and cycles of one day. The markov model is preceded by a 2 month primary phase. Patients going into the primary phase are youths with sub optimal symptom control from methylphenidate immediate release, but from this group only those who are responding to immediate release methylphenidate but the treatment is suboptimal due to inefficient exposure because of the multiple daily administration required go into the markov phase. Staying on IR MPH is then compared to optimal response with OROS MPH. There are 4 states in each arm (not the same for both arms).</p> <p>Perspective: Dutch Societal perspective Time horizon: 10 years Treatment effect duration:^(a) 10 years Discounting: Costs: 4%; Outcomes: 4%</p>	<p>treatment with IR MPH)</p> <p>Markov phase: children and young people responding sub optimally to IR MPH because of inappropriate intake. (assumed 83% of the 42% above)</p> <p>Cohort settings: Start age: age of 8 Male: NR</p> <p>Intervention 1: Immediate release methylphenidate (IR MPH)</p> <p>Intervention 2: Osmotic release methylphenidate (OROS MPH)</p>	<p>(95% CI: NR; p=NR)</p> <p>Currency & cost year: [2005 Dutch Euros (presented here as 2005 UK pounds^(b))]</p> <p>Cost components incorporated: Medication costs Consultation costs (with GP's, specialists, and crisis contact) Other intervention costs (e.g. psycho education, parent training, behaviour therapy, teacher training. Special education is also included here but these costs have been subtracted from the cost effectiveness in this table.</p> <p>Special education costs were subtracted from the total costs shown in this table.</p>		<p>Analysis of uncertainty: A series of univariate sensitivity analyses were performed on most of the model parameters. This involved varying base case values +/-25%. In addition a 'worst case scenario' ICER was derived combining all variation of the base case ICER. A best case ICER was also derived. The parameters that affected the ICER the most were resource use in the optimal and suboptimal states, and the probability of stopping treatment. the cost of OROS methylphenidate also had a big impact on the ICER.</p> <p>A worst case ICER was around £30,000, and the best case scenario was the OROS pathway being dominant.</p>
Data sources				

Study	[Faber 2008 ²²¹]
<p>Health outcomes: the 4 health states for the IR MPH pathway include; suboptimal response, optimal response, treatment stopped, and functional remission. The OROS pathway included 4 health states of; optimal response, non-compliance, treatment stopped, and functional remission. An expert panel of 5 clinicians (3 paediatricians and 2 child psychiatrists) were used to derive information on resource use, proportions of people responding/not responding, mean doses, frequency of consultations.</p> <p>The expert panel estimated that 19.3% of youths in the suboptimal response state might become optimal responders in the first year of treatment (or 0.053% per day) it was assumed that this would decline linearly to 0% after 10 years follow up. The probability of youths using OROS MPH being non-compliant for 1 day was derived from a RCT (at the end of 8 weeks 56% missed at least one dose with a total number of missed doses of 1.9, so based on these figures a probability of non-compliance to OROS of 0.019 per day was derived. Duration of stimulant use was estimated from the pharmacy dispensing database which includes most patients' records; duration of stimulant use was estimated for all users aged 5-9 in 2000-2002 for those who had not received a prescription for stimulants for more than 180 days, using Kaplan Meier survival estimates. A discontinuation hazard was found of 0.0003 per day for the first 180 days followed by a hazard of 0.0002 per day (this was the same for IR and OROS in the base case). The probability of functional remission of ADHD per day was derived from a study (Biederman 2000) which found functional remission (loss of partial diagnostic status plus functional recovery) was 10% in the oldest age group and so 10% functional remissions over 12 years was assumed which implies a probability of 0.00002 per day. This was assumed to be constant over time.</p> <p>Quality-of-life weights: utilities were from a UK study by Secnick 2005⁵⁶¹, using parents of children with ADHD using the standard gamble method to elicit preferences. Health states differentiated between types of stimulants like immediate or modified release. Utilities included were as follows; IR MPH responder (0.913), OROS MPH responder (0.93), non-responder on no medication (0.899), suboptimal state (0.901), remission (1), non-compliance (0.899).</p> <p>Cost sources: note that medication costs during the primary phase were recorded in the model. Mean daily doses assumed for ages 8 and 18 by the panel of experts, and this was increased linearly over the 10 year period. The OROS dose was assumed as being 20% higher than the IR MPH as stated in the prescribing info. For youths in the optimal response state a pharmacy fee of €6.10 per 3 months was included. For suboptimal response states the pharmacy is assumed to be every 4 months. No medication costs were incurred in non-compliance, treatment stopped, and remission states. Assumed costs of non-pharmacological interventions were incurred in years 1 and 6 of treatments. Medication costs were from the health care insurance board. Most other intervention costs (such as non-pharmacological therapies, special education, outpatient treatment) were from other national sources. Estimates of other resource use such as number of consultations per year were from the panel of experts. The treatment stopped state had the highest number of consultations.</p> <p>The cost components of the total cost are presented separately, so the special education costs can be subtracted as these will not be healthcare costs.</p>	
Comments	
<p>Source of funding: Janssen Cilag (makers of Concerta). Limitations: Non UK, uses different but similar discount rates, does not use EQ-5D and utilities not from the public. Potential conflict of interest. A lot of assumptions/inputs from a panel of experts and limited data. Other: the ICER has been calculated by the health economist as the special education costs were subtracted, then the currency converted. So the difference has been calculated post currency conversion and divided by the incremental QALY gain.</p>	
<p>Overall applicability: partially applicable^(c) Overall quality: potentially serious limitations^(d)</p>	

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; IR MPH: immediate release methylphenidate, OROS MPH: osmotic controlled release methylphenidate

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2005 purchasing power parities⁴⁸⁶

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Pink highlighted text in the next two evidence tables indicate how those studies differ from the Faber study, which they are an adaptation of.

Study	[Van der Schans 2015 ⁶⁴³]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALYs)</p> <p>Study design: probabilistic decision model</p> <p>Approach to analysis: Markov model with a 10 year time horizon and cycles of one day. The markov model is preceded by a 2 month primary phase. This 2 month phase was considered the time interval that a patient was identified as a true non-responder or as a potential suboptimal responder but with compliance being the problem. This group of potential responders then went on to be in the markov. Staying on IR MPH</p>	<p>Population: In primary phase: Children and young people who show sub optimal symptom control with IR MPH (assumed 42% of youths starting treatment with IR MPH) Markov phase: children and young people responding sub optimally to IR MPH because of inappropriate intake. (assumed 83% of the 42% above)</p> <p>Cohort settings: Start age: age of 8 Male: NR</p> <p>Intervention 1: Immediate release</p>	<p>Total costs (mean per patient): Intervention 1: £8,862 Intervention 2: £9,459 Intervention 3: £8,413</p> <p>Incremental (2-1): £597 (95% CI: NA; p=NA) Incremental (3-1): -£449 (95% CI: NA; p=NA)</p> <p>Currency & cost year: [2013 Dutch Euros (presented here as 2013 UK pounds^(b))]</p> <p>Cost components incorporated: Medication costs Consultation costs (with GP's, specialists, and</p>	<p>QALYs (mean per patient): Intervention 1: 6.855 Intervention 2: 7.173 Intervention 3: 7.173</p> <p>Incremental (2-1): 0.318 (95% CI: 0.053, 1.285; p=NR) Incremental (3-1): 0.318 (95% CI: 0.061, 1.313; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1): £1,879.37 per QALY gained (da) 95% CI: NA Probability Intervention 2 cost-effective (£20K/30K threshold): NA</p> <p>ICER (Intervention 3 versus Intervention 1): Intervention 3 is dominant 95% CI: NA Probability Intervention 3 cost-effective (£20K/30K threshold): NA</p> <p>(note that the probabilities of being cost effective and confidence intervals around the ICERS are not applicable here because the ICER reported in the paper is not the one reported here as some non-health costs have been deducted here)</p>

Study	
<p>is then compared to switching to modified release versions; OROS MPH, or Medikinet CR/Equasym XL (these two interventions were grouped together). There are 4 states in each arm (the same for both arms).</p> <p>Perspective: Dutch Societal perspective Time horizon: 10 years Treatment effect duration:^(a) 10 years Discounting: Costs: 4%; Outcomes: 1.5%</p>	<p>[Van der Schans 2015⁶⁴³]</p> <p>methylphenidate (IR MPH)</p> <p>Intervention 2: Extended release methylphenidate: Osmotic release methylphenidate (OROS MPH)</p> <p>Intervention 3: Extended release methylphenidate: Medikinet CR/Equasym XL</p>
<p>crisis contact)</p> <p>Other intervention costs (e.g. psycho education, parent training, behaviour therapy, teacher training.</p> <p>Indirect costs; direct healthcare costs of mother and productivity losses.</p> <p>Special education costs and indirect costs have been subtracted from the cost effectiveness in this table. (had indirect costs been reported separately as costs to the mother and productivity losses, then only productivity losses would have been excluded)</p>	<p>Analysis of uncertainty:</p> <p>A series of univariate sensitivity analyses were performed on most of the model parameters. This involved varying base case values +/-25%. In addition a multivariate sensitivity analysis was performed where the worst case parameter values were analysed.</p> <p>The parameter most likely to alter the results was the percentage of patients benefitting from switching from IR MPH to one of the extended release versions.</p>
Data sources	
<p>Health outcomes: The 4 health states were; suboptimal responder, optimal responder, discontinuing treatment, and natural remission. An expert panel of 5 clinicians (3 paediatricians and 2 child psychiatrists) were used to derive information on resource use, proportions of people responding/not responding, mean doses, frequency of consultations. It was assumed by switching to a modified release version, 83.6% would become an optimal responder (Gau et al). In the Faber model 100% were assumed to become optimal responders. There was no transition from optimal to suboptimal response in the IR MPH arm. A new addition in this model is the probability of restarting treatment (defined as a gap of 6 months or more between prescriptions). The restarting rate was assumed at 11% the first year after stopping, 4% in the second, in the third and fourth an increase of 3% was modelled until a max of 18% was reached. There was no likelihood of restarting in the last six years of the model. All other transition probabilities were the same as Faber.</p> <p>Quality-of-life weights: utility weights were from a study that derived utilities from the general population using the Time Trade-Off method. Utilities applied were; sub-optimally treated (0.70), optimally treated (0.82), treatment stopped (0.65), remission (1).⁴¹⁴</p> <p>Cost sources: direct costs (consultation, intervention, and special education costs) were derived from the Faber paper with an inflation adjustment applied to convert the costs to 2013 prices. Medication costs were from the health care insurance board. Average daily doses were calculated using prescription data. Indirect costs (direct medical costs of the mother and reduced costs due to absenteeism and reduced efficiency at work) were added based on a study (Le et al) that looked at the indirect costs of people with and without ADHD. Indirect costs were attributed to the health states by weights</p>	

Study	[Van der Schans 2015⁶⁴³]
based on the ratio of direct costs of the different health states. Patients discontinuing were attributed 100% of indirect costs (€2,517), optimal responders; 21.7% (€546), suboptimal responders; 42.9% (€1,081).	
Comments	
Source of funding: A Netherlands organisation for health research and development grant. Limitations: Non UK, uses different discount rates. Potential conflict of interest as some authors have received grants from companies that make some of the products. A lot of assumptions/inputs from a panel of experts and limited data. Other: the ICER has been calculated by the health economist as the special education costs and indirect costs were subtracted, then the currency converted. So the difference has been calculated post currency conversion and divided by the incremental QALY gain. Not clear if base case results are probabilistic or not. The probabilities for the two modified release methylphenidate arms are the same so the main difference is drug costs.	
Overall applicability: partially applicable ^(c) Overall quality: potentially serious limitations ^(d)	

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; IR MPH: immediate release methylphenidate, OROS MPH: osmotic controlled release methylphenidate

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2013 purchasing power parities⁴⁸⁶

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[Schawo 2015⁵⁵⁶]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALYs)</p> <p>Study design: probabilistic decision model</p> <p>Approach to analysis: Markov model with a 12 year time horizon and cycles of one day. Staying on IR MPH is then compared to switching to</p>	<p>Population: Patients who had responded sub-optimally to IR MPH because of incorrect intake of medication.</p> <p>Cohort settings: Start age: age of 6 Male: NR</p> <p>Intervention 1:</p>	<p>Total costs (mean per patient): Intervention 1: NR Intervention 2: NR</p> <p>Incremental (2-1): -£4,231 (95% CI: NA; p=NA)</p> <p>Currency & cost year: [2014 Dutch Euros (presented here as 2014</p>	<p>QALYs (mean per patient): Intervention 1: NR Intervention 2: NR</p> <p>Incremental (2-1): 0.15 (95% CI: NR; p=NR)</p> <p>The incremental QALY for the sensitivity analysis that excluded caregiver utility is</p>	<p>ICER (Intervention 2 versus Intervention 1): Intervention 2 is dominant. 95% CI: NA Probability Intervention 2 cost-effective (£20K/30K threshold): NA</p> <p>Analysis of uncertainty: 1000 monte carlo simulations. Four scenarios were tested as</p>

Study	[Schawo 2015 ⁵⁵⁶]			
<p>OROS MPH. There are 4 states in each arm (the same for both arms).</p> <p>Perspective: Dutch Societal perspective</p> <p>Time horizon: 12 years</p> <p>Treatment effect duration: ^(a) 12 years</p> <p>Discounting: Costs: 4%; Outcomes: 1.5%</p>	<p>Immediate release methylphenidate (IR MPH)</p> <p>Intervention 2: Extended release methylphenidate: Osmotic release methylphenidate (OROS MPH)</p>	<p>UK pounds^(b)]</p> <p>Cost components incorporated:</p> <p>Medication costs Consultation costs (with GP's, specialists, and crisis contact) Other intervention costs (e.g. psycho education, parent training, behaviour therapy, teacher training. Indirect costs; direct healthcare costs of mother and productivity losses.</p> <p>The incremental cost from one of the sensitivity analyses is being reported here as the base case cost because it excludes medical costs and production loss costs of the caregiver. Had these been reported separately then only the production loss costs would have been excluded. Therefore still also includes special education costs.</p>	<p>reported here, as the addition of utility to the patient because of the resultant impact on the parent's utility was only assumed and not derived from actual preference data, therefore this has been excluded in this base case result.</p>	<p>sensitivity analyses;</p> <ul style="list-style-type: none"> - assuming transition rates are equal for the two interventions. - Including an augmented daily dose of exposure to medication (to account for noncompliance in the dose data used in the base case; which was based on real data). - excluding medical costs and production losses of the caregiver (incremental costs of this analysis assumed as the base case here) - excluding the utility of caregivers (incremental QALYs of this analysis assumed as the base case here). <p>All analyses resulted in cost savings and increased QALYs for MPH OROS, except for when transition rates of OROS were assumed equal to IR MPH. This analysis also resulted in zero incremental QALYs.</p>
Data sources				
<p>Health outcomes: The 4 health states were; suboptimal responder, optimal responder, treatment stopped, and natural remission (although transitions to remission were assumed to be zero by the experts so this state is redundant). A panel of 4 experts estimated all the transition probabilities using Delphi surveys, and these were applied throughout the 12 year time horizon. A mean of 3 doses per day of IR MPH and 1 per day of OROS was assumed.</p>				

Study	[Schawo 2015⁵⁵⁶]
<p>Quality-of-life weights: quality of life was from a study (Van der kolk et al 2014⁶³⁹) that used parent proxy ratings using the EQ-5D. Quality of life for the compliant patients from this study were used for the 'optimal' state, and the utilities for the non-compliant group for the 'sub-optimal' state. Patient who stopped treatment were assumed to have the same utility as for the sub-optimal state.</p> <p>Indirect utility: Also included spillover effects on the utility of the parent; they included 48% of caregiver utility in the model (this seems to be applied on top of the patients utility as if the patients quality of life improves then this is also assumed to improve the quality of life of the carer). This is based on evidence suggested for meningitis and not quality of life elicitation for the carers.</p> <p>Cost sources: cost categories were consistent with the Faber model; medication costs, consultation costs, costs of medical and non-medical interventions, costs of special education. In remission assumed no costs associated with ADHD. Assumed all costs except drug costs to be dependent on the state and not on the treatment. Assumptions about resource use in different states for the different age groups (below and above 12) were taken from the Faber paper. Unit prices were from the Dutch manual for costing. Costs of special education were updated as reported by the Dutch Ministry of Education and costs adjusted to 2014 values. Costs in 2014 Euros. Cost of medication was based on Dutch price list. Justice costs were looked for but not included. Indirect costs: Spillover costs onto the caregiver were included from Hakkart van Roijen et al which found healthcare costs of mothers of children with ADHD were higher than those without and stated that 25% of mothers noted their use of healthcare services was related to behavioural problems of the child , so 25% of the difference in costs found in the study of annual medical costs of the mother were included in the model (€165.96) in the suboptimal and treatment stopped states (no additional costs in the optimal state). Mean annual production losses for the mother were also included in the suboptimal and treatment stopped state of (€453.64).</p>	

Comments	
<p>Source of funding: Janssen-Cilag. Limitations: Non UK, uses different discount rates. Potential conflict of interest. A lot of assumptions/inputs from a panel of experts and limited data. Other: what is different in this model compared to the Faber paper is updated utility estimates, a probabilistic model, changes in; health states, start age in model, time horizon, transition probability estimates, caregiver costs.</p> <p>Overall applicability: partially applicable^(c) Overall quality: Very serious limitations^(d)</p>	

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; IR MPH: immediate release methylphenidate, OROS MPH: osmotic controlled release methylphenidate

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2014 purchasing power parities⁴⁸⁶

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[Lachaine 2016³⁹⁴]			
Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness

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<p>Economic analysis: CEA/CUA (health outcome: QALYs, patient weeks with a response)</p> <p>Study design: Probabilistic decision model</p> <p>Approach to analysis: Two stage markov model with a 1 year time horizon and weekly cycles. Four health states based on the CGI-S. Looks at a population of children who are partial responders to long acting stimulants and compares staying on long acting stimulants versus adding Guanfacine as an adjunct.</p> <p>Perspective: Canadian Ministry of Health</p> <p>Time horizon/Follow-up: 1 year</p> <p>Treatment effect duration:^(a) 1 year</p> <p>Discounting: Costs: NA; Outcomes: NA</p>	<p>Population: Children aged 6-12 with ADHD with a sub-optimal response to stimulants.</p> <p>Cohort settings: Start age: NR Male: 71.6% (based on trial used for effect) Proportion starting in each state: Normal;0.00 %, Mild; 3.52 %, Moderate; 90.55 %, Severe; 5.93 %</p> <p>Intervention 1: Long-acting stimulant monotherapy</p> <p>Intervention 2: Guanfacine extended release (GXR) + long-acting stimulant</p> <p>(doses not reported as dose use for costs are doses used in practice using real data, but effectiveness of interventions is based on doses in the trial the model is based on).</p>	<p>Total costs (mean per patient): Intervention 1: £530 Intervention 2: £902 Incremental (2-1): £373 (95% CI: NR; p=NR)</p> <p>Currency & cost year: 2013 Canadian dollars (presented here as 2013 UK pounds^(b))</p> <p>Cost components incorporated: Medication costs, primary care visits, mental health visits, pharmacy fills, emergency department visits and hospitalizations</p>	<p>QALYs (mean per patient): Intervention 1: 0.627 Intervention 2: 0.655 Incremental (2-1): 0.028 (95% CI: NR; p=NR)</p> <p>Patient weeks with a response: Intervention 1: 12.46 Intervention 2: 19.03 Incremental (2-1): 6.57 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1): £13,321 per QALY gained (pa) 95% CI: NR</p> <p>Probability Intervention 2 cost effective: 95% (read off a graph at a point of \$CA36,000 which would be around £20,000)</p> <p>Analysis of uncertainty: Probabilistic sensitivity analysis with 10,000 simulations.</p> <p>Several one-way sensitivity analyses were performed by varying a single variable individually within lower and upper bounds of all key parameters. More specifically, sensitivity analysis on;</p> <ul style="list-style-type: none"> - transition probabilities were performed using the observed transitions between the health states during the first 8 weeks and assuming that health states were stabilized without further transitions in the second stage of the model. - In the base-case model, ordered logit models were used to estimate the transition probabilities. A last observation carried forward (LOCF) technique was used in sensitivity analysis to obtain transition probabilities. - In Canada it may be harder to access long-acting stimulants so to take this into account, a sensitivity analysis comparing GXR adjunctive therapy to short/intermediate- acting stimulants with placebo plus short/intermediate- acting
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			<p>stimulants was performed by varying only the stimulant drug costs.</p> <p>The parameters with the greatest impact on base-case ICERs from the MoH perspective were (i) the calculation of transition probabilities based on trial data for the first 8 weeks and then LOCF for the remainder of the study period and (ii) the initial health state distribution assuming 100 % of patients started in the severe state.</p> <p>In a sensitivity analysis where patients were maintained on treatment and could transition between health states during the weeks 9-52 period the ICER increased to \$47,909 (almost £27,000) from a MoH perspective.</p>
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Data sources

Health outcomes: Treatment effect was based on a single trial where GXR or placebo was co-administered to a long-acting stimulant in patients who had a suboptimal response to stimulants alone⁶⁹⁰. Suboptimal response was defined as; ≥4 weeks of a stable dose of treatment with an extended-release stimulant with improvement but continued mild to moderate symptoms of ADHD; ADHD-RS-IV total score of ≥24 and a CGI-S ≥3; and investigator assessment of inadequate response to current stimulant. To represent the Canadian situation, only long-acting stimulants available in Canada were considered in the base-case model. A methylphenidate-based stimulant available in Canada but not in the US was not assessed in the effectiveness study and so a similar efficacy for that and other methylphenidates included in the pivotal study was assumed. The model structure was a two stage markov model over a 1 year time horizon with weekly cycles. Health states were based on the clinician reported CGI-S; severe (CGI-S score of “Severely ill” or “Among the most extremely ill subjects”), moderate (CGI-S score of “Moderately ill” or “Markedly ill”), mild (CGI-S score of “Borderline ill” or “Mildly ill”) and normal (CGI-S score of “Normal”). Patients’ starting health state was based on the distribution of starting CGI-S scores in the trial across the treatment arms. Consistent with the trial period, the first stage of the model was assumed to span from week 0 to week 8, and the second stage extended from week 9 to week 52. All patients remained on treatment during the first stage of the model. Thereafter, patients in the moderate or severe states at week 8 were considered to be non-responsive and therefore permanently discontinued their treatments. As most of the patients included in the trial had moderate or severe disease at baseline, remaining with a moderate or severe disease after 8 weeks would indicate a lack of response to treatment. Similarly, patients who transitioned into the moderate or severe state during the second stage of the simulation (weeks 9–52) discontinued treatment and remained in the last observed health state for the rest of the model period. In a sensitivity analysis, patients were maintained on treatment and could transition between health states during the weeks 9–52 period. The transition probabilities between health states were taken from the patient-level data from the effectiveness study. Following the trial definition of endpoint, the efficacy data from the first 8 weeks were used. Patients were assigned each week to one of the four

health states from week 0 to week 8 based on the observed weekly CGI-S values. In the base-case model, ordered logit models were used to estimate the transition probabilities, where the dependent variable was the current health state and the independent variable was the health state in the previous week. Transition probabilities were estimated for the placebo plus stimulants arm and the combined GXR plus psychostimulants arm. The estimated transition probabilities were applied throughout the model period for patients remaining on treatment. The population in the trial was actually children aged 6-17 but because the product label for GXR is for those aged 6-12, an age of 6-12 was used in this model assuming the effect would be the same as that of the trial. Adverse events were also included – not much info on how these were applied but incidences and methods were probably same as US economic evaluation this model was adaptation of ⁵⁷¹.

Quality-of-life weights: Lloyd 2011⁴¹⁴; used time trade-off to elicit quality of life based on descriptive health states (matching the CGI-S) from 100 members of the UK public. Utilities used for each health state were; Normal; 0.839, Mild; 0.787, Moderate; 0.578, Severe; 0.444.

Disutilities were also applied to adverse events. The incidence of adverse events for each intervention and the disutility associated with each was reported in the US economic evaluation that this Canadian economic evaluation is an adaptation of ⁵⁷¹. AEs were assumed to result in a utility decrement lasting for 4 weeks.

Cost sources: A weighted average of the costs and type of long acting stimulants used in Canada was used to derive the cost of stimulants. The unit cost of GXR for each available dose was taken from the Quebec’s Medication List, while the daily cost of each long-acting stimulant was based on daily dose and number of pills according to Canadian data from IMS Brogan for children aged 0–12 years. The unit cost of each dose of long-acting stimulant was taken from the Ontario Drug Benefit Formulary. Costs associated with health care resources used in the management of ADHD were based on a study by Guevara et al. In this study, resource utilization of specific categories of health care services including primary care visits, mental health visits, pharmacy fills, emergency department visits and hospitalizations were estimated for children with and without ADHD. Unit costs from Canadian sources were applied to the additional resource use estimates associated with ADHD (resource use for children with ADHD – resource use for children without ADHD) to obtain the cost associated with each category of health care service. The mean cost of a script in Canada was obtained from IMS Health Canada and was a weighted average of the mean cost per script of brand and generic products. The same number of non-ADHD pharmacy fills was applied to all patients. Medical costs derived from the study by Guevara et al. were allocated according to disease severity. More specifically, the annual medical costs for patients in the “normal” health state were assumed to be the same as the median medical costs for non-ADHD patients (\$CA245). The cost of the “mild” subgroup has been estimated as follows: the median cost for a patient with ADHD is \$CA322 and the minimal cost for an ADHD patient is \$CA245 (cost without ADHD). Assuming a linear distribution, the annual cost of the 3.52th patient (the initial proportion of patients in the “mild” state was 3.52 %) was estimated at \$CA250. Thus, the average cost for the “mild” subgroup was \$CA248 (mean of \$CA245 and \$CA250). To properly represent the skewness of the data, the costs incurred by the “severe” patients were assumed to be two times the mean cost estimated from Guevara et al. (\$CA738). Therefore, the annual cost in the “severe” group was estimated at \$CA1,476. The average annual cost in the “moderate” subgroup was then calculated using the cost estimates of the “mild” and “severe” states and to retrieve the original mean cost estimated from Guevara et al. according to the initial distribution of patients. Therefore the mean annual cost incurred by the “moderate” state was estimated at \$CA709. A societal perspective was also used with productivity losses included, but as these results were reported separately and this is not a perspective relevant to the NHS this result has not been reported.

Comments

Source of funding: Shire. **Limitations:** Canadian cost perspective. Uses utilities based on TTO direct elicitation. Potential conflict of interest. Assumptions about extrapolation of effect. Effectiveness based only on one trial which is only 9 weeks. **Other:**

Overall applicability: Partially applicable^(c) **Overall quality:** Potentially serious limitations^(d)

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; CGI-S: Clinical Global Impression-Severity; MoH: Ministry of Health

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2013 purchasing power parities⁴⁸⁶

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	[Zimovetz 2016 ⁷¹⁵]			
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALYs)</p> <p>Study design: Probabilistic decision analytic model</p> <p>Approach to analysis: Decision tree model with 1 year time horizon comparing lisdexamfetamine (LDX) to atomoxetine (ATX) in children who had an inadequate response to methylphenidate (MPH). People can either tolerate or not tolerate the treatment, and then those who tolerate can either respond or not respond. Treatment effect based on a single head to head 9 week</p>	<p>Population: Children and adolescents with ADHD in whom a response to methylphenidate was considered clinically inadequate.</p> <p>Cohort settings: Start age: NR Male: NR</p> <p>Intervention 1: Atomoxetine</p> <p>Intervention 2: Lisdexamfetamine</p> <p>(doses NR as were based on the doses from the single trial the model is based on).</p>	<p>Total costs (mean per patient)^(b): Intervention 1: £2,332 Intervention 2: £2,352</p> <p>Incremental (2-1): £20 (95% CI: NR; p=NR)</p> <p>Currency & cost year: 2012 UK pounds</p> <p>Cost components incorporated: - Drug costs - Other resource use; consultations with psychiatrists/ paediatricians/GP/nurse, blood tests, ECG's.</p>	<p>QALYs (mean per patient)^(b): Intervention 1: 0.8092 Intervention 2: 0.8202</p> <p>Incremental (2-1): 0.011 (95% CI: NR; p=NR)</p>	<p>ICER (Intervention 2 versus Intervention 1): £1,586 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K threshold): 86%</p> <p>Analysis of uncertainty: PSA with 1000 simulations. Two alternative scenarios were also performed probabilistically using the base case inputs; one using efficacies from the MTC and one using utility weights from the direct trial.</p> <p><i>One way sensitivity analyses varied;</i> Response rates:</p> <ul style="list-style-type: none"> Using the ADHD-RS cut off of reduction of >=25%, using a non-response imputation method. This is more of a conservative approach than the base case because also the LDX response rate decreased whilst the ATX rate stayed similar. Using response rates from an MTC conducted using ADHD trials in a broader

<p>trial of the two drugs. Includes healthcare resource use of responders and non-responders.</p> <p>Perspective: UK NHS Time horizon/Follow-up: 1 year Treatment effect duration:^(a) 1 year Discounting: Costs: NA ; Outcomes: NA</p>				<p>group (not just second line studies). Utility values:</p> <ul style="list-style-type: none"> Using utilities from Lloyd 2011⁴¹⁴, which used a time trade-off method to elicit utilities based on CGI-S health states and mapped these to CGI-I health states for responders and non-responders. Using utilities directly from the head to head trial, using the HUI2 measure. <p>Resource use estimates:</p> <ul style="list-style-type: none"> The resource use estimates in the base case were replaced by those from the King HTA model. Additional sensitivity analyses varying the percentage of visits that were assumed to be consultations with junior doctors instead of psychiatrists/paediatricians. <p>Drug costing method:</p> <ul style="list-style-type: none"> Doses were used using real world data from Canada and Brail where LDX was already used. <p>For the additional two PSA scenarios; LDX was dominant using the MTC estimate, and had an ICER of £4,968 when using the head to head trial utilities. LDX remained cost effective in all sensitivity analyses and was dominant in two of them; assumptions about drug costs, and using MTC effectiveness.</p>
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Data sources

Health outcomes: Patients begin the drug when they enter the model. Titration period lasts 28 days. Patients who experience intolerable side effects discontinue treatment in the middle of the titration period (after 14 days). Patients who discontinue during the titration period are applied the utilities and healthcare (non-drug) costs of a 50%/50% of responders and non-responders. These people do not initiate additional treatment and are applied the same costs and utilities as non-responders for the remaining time horizon. Patients who respond continue to receive treatment and remain responders. At the end of titration, non-responders discontinue all drug treatments and remain non-responders for the remaining time horizon. It was assumed that patients

from the trial who responded with treatment remained adherent over the time horizon of the model. Efficacy and safety data both come from a 9 week trial comparing LDX and ATX in children who were inadequate responders to MPH, Dittmann 2013²⁰⁷ where 81.7% of children responded to LDX at week 9 on the CGI-I compared to 63.6% in the ATX arm, using the last observation carried forward method. These values were used in the model base case. Tolerability in the model was based on the rates of withdrawal because of adverse events (6.3% for LDX and 7.5% for ATX). **Quality-of-life weights:** Utilities were from Coghill 2004¹⁶⁸, using EQ-5D, based on responders or not to drug treatment. 0.773 for non-responders, and 0.837 for responders. **Cost sources:** Drug costs from the BNF 2012. Healthcare resource use associated with response and non-response was from a survey of UK clinicians (21 specialists). The items of healthcare resource use were based on those reported by the King HTA³⁷¹ in their model. Total average resource use cost per year used in the model was £1,297 for responders and £2,473 for non-responders. Drug doses were the mean doses for the titration and maintenance period reported in the Dittmann trial. Drug costs; LDX: £83.02 during titration and £72.28 per 28 days post titration, ATX: £82.43 during titration and £63.03 per 28 days post titration.

Comments

Source of funding: Funded by Shire (manufacturer of Elvanse – a brand of LDX. **Limitations:** UK perspective. EQ-5D. Limitations include: Potential conflict of interest because of funders. Some structural components that may not reflect reality. Assumptions about extrapolation of effect. Effectiveness based only on one trial which is only 9 weeks and could be argued that effect of comparator may be underestimated. SA uses MTC data but this is again data funded by the manufacturer of the intervention. **Other:** the paper states that individual adverse events data were not used from the trial because these were similar between the two groups. The MTC used for the response rates in a sensitivity analysis was also funded by Shire and was looking at comparing LDX to other drugs, so still a conflict of interest there to favour LDX.

Overall applicability: Directly applicable^(c) **Overall quality: Potentially serious limitations**^(d)

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; HUI2: Health Utilities Index mark 2, a preference based generic utility measure, like the EQ-5D this is on a 0 to 1 scale; TTO: time trade-off – a method of directly eliciting preferences to find utilities that involves asking people questions about trading off different health states against each other until the person is indifferent to the alternatives offered which then generates the utility value; MTC: mixed treatment comparison.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Note that the total costs and QALYs reported are deterministic because only the ICER was reported probabilistically, not the individual costs and QALYs.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

I.1.1 Pharmacological efficacy

Table 132: Studies excluded from the clinical review

Study	Exclusion reason
Abbasi 20112	Incorrect interventions
Abikoff 20074	Less than minimum duration
Adler 200818	No usable outcomes
Adler 200819	Open label
Adler 200920	No relevant outcomes
Adler 201113	Incorrect interventions
Adler 201114	Open label
Adler 20145	No relevant outcomes
Adler 20146	Incorrect interventions
Adler 201615	Incorrect population
Agay 201023	No relevant outcomes
Agay 201424	No relevant outcomes
Aman 200032	Incorrect study design
Aman 200427	Participants permitted to continue concomitant ADHD medication
Aman 200829	Incorrect study design
Aman 200930	Inappropriate comparison
Aman 200933	No control group
Aman 201031	Abstract
Aman 201428	Incorrect interventions
Aman 201526	Incorrect study design
Amiri 201336	not RCT
An 201337	No relevant outcomes
Anderson 200738	Not article
Anon 19991	Incorrect interventions
Anon 2002631	Incorrect study design
Anonymous 200839	Incorrect study design
Anonymous 2009247	Not article
Anonymous 2016176	Not in English
Apostol 201240	Incorrect intervention
Araki 201542	Inappropriate comparison
Armenteros 200743	Incorrect interventions
Armstrong 201244	Time treatment interaction
Arnold 200746	Incorrect intervention
Arnold 201047	Open label
Arnold 201048	Parent study excluded
Arnold 201549	Wrong intervention (combination)
Asherson 201551	Systematic review: study designs inappropriate

Study	Exclusion reason
Ashkenasi 201152	Open label
Babinski 201454	Incorrect interventions
Babinski 201456	Studies including participants who have previously received medication for ADHD, or studies where response to previous treatment is an inclusion criteria . No relevant outcomes
Babinski 201655	Incorrect population
Bahcivan saydam 201557	No intervention
Bain 201258	Incorrect interventions
Bain 201359	Incorrect interventions
Banaschewski 2014 60	Studies where response to previous treatment is an inclusion criteria: "Key exclusion criteria for all patients included failure to respond to previous osmotic-release oral system methylphenidate (OROS-MPH) therapy"
Bangs 200863	Abstract
Barbaresi 201464	Incorrect study design
Barkley 200765	Incorrect interventions
Barnard 200266	Review: references checked
Barry 200668	Incorrect study design. Commentary
Bart 201069	No relevant outcomes
Barton 200670	Incorrect study design
Becker 201372	Background info
Becker 201671	Incorrect study design
Bedard 200874	No relevant outcomes
Bedard 201573	No relevant outcomes
Bendz 201075	Incorrect study design
Bental 200876	No relevant outcomes
Benvenuto 201377	Incorrect study design
Berlin 201278	Incorrect interventions
Beyer von morgenstern 201479	Incorrect study design
Biederman 1989 82	Studies where response to previous treatment is an inclusion criteria: 69% previously responded poorly to psychostimulant treatment
Biederman 1989 81	Studies where response to previous treatment is an inclusion criteria: 69% previously responded poorly to psychostimulant treatment
Biederman 1993 80	Studies where response to previous treatment is an inclusion criteria: 69% previously responded poorly to psychostimulant treatment
Biederman 200286	Subgroup analysis
Biederman 2005 96	Studies where response to previous treatment is an inclusion criteria: "Patients whose ADHD was well controlled and who were satisfied with current ADHD therapy were also excluded, as were those who had failed to respond to 2 or more adequate courses of stimulant therapy for ADHD"
Biederman 200794	Meta-analysis: references checked
Biederman 200792	No relevant outcomes
Biederman 200783	No relevant outcomes
Biederman 200893	Meta-analysis of individual studies included in review

Study	Exclusion reason
Biederman 200888	Open label
Bilder 201697	No relevant outcomes
Blader 200999	Incorrect interventions
Blader 201398	Inappropriate comparison
Blum 2011101	No relevant outcomes
Blumer 2009102	Incorrect interventions
Boellner 2010103	Inappropriate comparison
Bögels 2008104	Incorrect interventions
Bohnstedt 2005105	Insufficient information on full trial
Boisjoli 2007106	Incorrect interventions
Boonstra 2007107	No relevant outcomes
Borsting 2008108	Conference abstract
Bottelier 2014109	Protocol
Brams 2008113	Crossover no washout, less than minimum duration
Brams 2010112	Review: references checked
Brams 2011111	Open label
Brams 2012114	Erratum
Brams 2012115	Dose comparison
Brams 2012116	No washout following open label lead in phase
Brown 1989119	No relevant outcomes
Brown 2010120	Open label
Brown 2010122	Meta-analysis of included studies
Bubnik 2015123	No relevant outcomes
Buchmann 2007124	Inappropriate comparison
Buitelaar 1996125	Incorrect study design
Buitelaar 1996130	Incorrect interventions
Buitelaar 2007126	Incorrect interventions
Buitelaar 2009127	Open label
Buitelaar 2012128	Open label
Burton 2015131	Not guideline condition
Butter 1983132	Less than minimum duration
Butter 1984133	Less than minimum duration
Camporeale 2013 135	Studies where response to previous treatment is an inclusion criteria: "Only atomoxetine responders were allowed to enter this study period; non responders were excluded from the study"
Cantilena 2012137	Less than minimum duration
Cardo 2013138	Open label
Castellanos-ryan 2013143	Incorrect interventions
Castells 2011144	Systematic review: checked for references
Cetin 2015145	Open label
Chang 2009147	Open label
Chang 2012148	No relevant outcomes
Chantiluke 2015149	No usable outcomes
Chantiluke 2015150	Incorrect study design
Chavez 2006151	Review: references checked
Chen 2014152	Studies where response to previous treatment is an inclusion

Study	Exclusion reason
	criteria: "Participants previously treated with stimulants were eligible, but subjects adequately maintained on any effective ADHD medication regimen were excluded"
Cheng-shannon 2004153	Review: references checked
Childress 2009 158	Inappropriate intervention
Childress 2012154	Open label
Childress 2014 157	Studies where response to previous treatment is an inclusion criteria
Childress 2015156	Inappropriate intervention
Ching 2012159	Systematic review checked for references
Cho 2011160	Open label
Chou 2017161	Non randomised study
Classen 2013163	Systematic review: study designs inappropriate
Classen 2013164	Incorrect study design
Classen 2013165	Incorrect study design
Coghill 2010166	Systematic review checked for references
Coghill 2014169	Systematic review: study designs inappropriate. open label
Cohen-yavin 2009173	Open label
Collins 2013174	Not article
Comer 2013175	Incorrect interventions
Connor 1994179	Incorrect study design
Connor 2013 182	Incorrect study design
Connor 2014180	References checked
Corkum 2008183	Crossover no washout
Cornforth 2010184	Review: references checked
Correia Filho 2005 185	Incorrect method of diagnosis
Cortese 2012186	No outcomes of interest
Costa 2013187	No relevant outcomes
Cottrell 2008188	Included in the economic review
Covey 2010191	Inappropriate comparison
Covey 2011189	No relevant outcomes
Covey 2015190	No useable outcomes
Cox 2008193	No relevant outcomes
Cox 2012192	Open label
Cubillo 2014194	No relevant outcomes
Cubillo 2014195	No relevant outcomes
Cutler 2010196	Conference abstract
Dean 2011201	Inappropriate comparison
Deputy 2002203	Not article
Devito 2009204	Incorrect study design
Dinca 2005205	Review: references checked
Dittmann 2009209	Open label
Doig 2008210	Incorrect study design
Donnelly 1986212	Incorrect population (diagnosis)
Dopfner 2011213	Less than minimum duration
Dupaul 2012214	Inappropriate comparison

Study	Exclusion reason
Durell 2010-1215	Subgroup analysis
Durell 2010-2215	Subgroup analysis
Epstein 2011219	Inappropriate washout period
Fabiano 2007222	Incorrect interventions
Fabiano 2010229	Incorrect interventions
Farah 2009223	Incorrect interventions
Farah 2009224	no relevant outcomes
Faraone 2007229	Incorrect intervention
Faraone 2009225	Review: references checked
Faraone 2009227	No data to extract
Faraone 2010226	Review: references checked
Faraone 2012228	Dose comparison
Farmer 2015230	Incorrect interventions
Farmer 2016231	No useable outcomes
Fernandez-jaen 2013232	Incorrect study design
Findling 2006241	Incorrect population
Findling 2007242	Crossover with no washout
Findling 2008235	Not article
Findling 2008237	Open label
Findling 2009244	Open label
Findling 2010233	Open label
Findling 2010239	Open label
Findling 2010243	Incorrect study design
Findling 2011236	Incorrect population
Findling 2013238	No comparator
Fitzpatrick 1990245	Incorrect study design
Flapper 2008246	Open label
Fortier 2013248	Inappropriate comparison
Foster 2007249	Incorrect interventions
Fox 2014250	No relevant outcomes
Fredriksen 2014251	Open label
Froehlich 2011253	no outcomes of interest reported
Froehlich 2014252	Incorrect duration
Fuentes 2013254	Open label
Fung 2016255	Review: references checked
Gadow 2011258	Incorrect study design
Gadow 2014 256	Open label
Gadow 2016257	Incorrect population
Gallucci 2006262	Incorrect study design
Garfinkel 1983263	Incorrect duration
Garg 2014264	Open label
Garg 2015265	Open label
Gau 2010267	Open label
Gawrilow 2016268	Incorrect interventions
Gehricke 2009269	Less than minimum duration

Study	Exclusion reason
Gehricke 2011270	Incorrect study design
Ghanizadeh 2012272	Incorrect intervention
Ghanizadeh 2012272	Incorrect intervention
Ghanizadeh 2012272	Incorrect intervention
Ghanizadeh 2013273	Incorrect interventions
Ghuman 2007275	Crossover no washout
Giblin 2011276	Less than minimum duration
Ginsberg 2011278	Open label
Ginsberg 2012280	Open label
Ginsberg 2014279	Open label
Gittelman-klein 1976282	Inappropriate method of diagnosis
Goez 2012283	No useable outcomes
Gonzalez-Carpio Hernandez 2016284	Incorrect study design
Gonzalez-heydrich 2010285	Less than minimum duration.
Grant 2015288	Conference abstract
Green 2011289	Less than minimum duration.
Greenhill 2003294	Incorrect interventions
Grizenko 2010296	Inappropriate comparison
Grizenko 2012297	Incorrect duration
Grizenko 2013295	Incorrect duration
Groom 2013298	Inappropriate comparison
Guardiola 1999299	Not in English
Gunther 2010300	No useable outcomes
Guo 2013301	Conference abstract
Gustafsson 2010302	Incorrect interventions
Haas 2008303	Open label
Haghighat 2014304	Not article
Hammerness 2009307	Review: references checked
Hammerness 2013306	Open label
Handen 2000309	Inappropriate washout period
Handen 2008310	Incorrect duration
Handen 2011311	Incorrect study design
Hardan 2005312	Incorrect study design
Harfterkamp 2013313	Open label
Harfterkamp 2015316	Post hoc. open label.
Hazell 2006318	Incorrect study design
Hazell 2009317	Inappropriate comparison. Less than minimum duration
Heffner 2013320	No relevant outcomes - weight
Hellwig-bridal 2011321	No relevant outcomes
Helseth 2015322	Incorrect study design
Heriot 2008323	Incorrect study design
Herring 2012324	Incorrect interventions
Hervas 2014325	Inappropriate method of diagnosis
Hester 2010326	No relevant outcomes
Hilton 2013327	Not guideline condition

Study	Exclusion reason
Hirata 2014328	Open label
Hoebert 2009329	Incorrect study design
Holden 2013330	Not guideline condition
Hong 2009331	Inappropriate comparison
Hong 2014332	Inappropriate comparison
Hosenbocus 2009333	Review: references checked
Howard 2015334	Incorrect interventions
Huizink 2009335	Incorrect interventions
Hurt 2011336	Non-ADHD population
Hurwitz 2012337	Systematic review: study designs inappropriate
Huss 2014338	Post hoc analysis
Huss 2014339	Studies where response to previous treatment is an inclusion criteria: "Patients with either hypersensitivity or history of poor response or intolerance to stimulants as per the investigator's judgement were excluded....responders [defined as patients with ≥30% improvement compared to baseline score on the DSM-IV ADHD Rating Scale who continued to meet inclusion criteria were re-randomized to enter the double-blind maintenance of effect phase"
Ialongo 1994341	Incorrect study design
Ironside 2010342	No relevant outcomes
Ishii-takahashi 2015343	Correction
Jacobi-polishook 2009344	No relevant outcomes
Jahromi 2009347	Inappropriate washout period
Jain 2007351	Studies where response to previous treatment is an inclusion criteria: "Patients were excluded from the study if they had a true allergy to methylphenidate or amphetamines; a history of serious adverse reactions to methylphenidate or were known to be non-responders"
Jain 2013349	Systematic review: study designs inappropriate
Jaselskis 1992353	Studies including participants who have previously received medication for ADHD, or studies where response to previous treatment is an inclusion criteria
Jasinski 2008354	Inappropriate washout period
Jasinski 2009355	no outcomes of interest reported
Jin 2013357	Open label
Johnston 2014358	Incorrect interventions
Jordan 2012359	Incorrect study design
Jucaite 2014360	Incorrect interventions
Kandemir 2014362	Background information
Kaplan 2004363	Subgroup analysis
Kaplan 2004363	Subgroup analysis
Kaplan 2004363	Subgroup analysis
Kay 2009364	Incorrect interventions
Keating 2011365	Not article
Kent 2013367	Open label
Keulers 2007368	Open label
Khodadust 2012369	brand not licensed

Study	Exclusion reason
Kim 2009370	Open label
King 2009372	Less than minimum duration
Koblan 2015373	Incorrect interventions
Kollins 2009375	No relevant outcomes
Kollins 2011377	Studies where response to previous treatment is an inclusion criteria: "children and adolescents with hyperactive- or combined-subtype ADHD who had an inadequate response to their stable stimulant regime"
Kollins 2013379	Incorrect comparison
Kollins 2014376	Incorrect comparison
Konstenius 2010381	Studies including participants who have previously received medication for ADHD, or studies where response to previous treatment is an inclusion criteria.
Konstenius 2013382	No useable outcomes
Konstenius 2013384	No useable outcomes
Konstenius 2013384	No useable outcomes
Konstenius 2013384	No useable outcomes
Konstenius 2014383	Incorrect interventions
Krakowski 1965387	Inappropriate method of diagnosis
Kratochvil 2007388	Studies where response to previous treatment is an inclusion criteria: all participants are non-responders to atomoxetine
Kubas 2012391	No useable outcomes
Kupietz 1988393	Incorrect population
Lamberti 2016395	Open label
Law 1999396	Incorrect interventions. (non-pharma combination)
Leblanc 2005397	Not guideline condition
Leddy 2009398	Genetics
Lee 2013399	No relevant outcomes - sleep
Lerer 1977402	Inappropriate washout period. Inappropriate method of diagnosis
Lerer 1979401	Inappropriate washout period
Leuchter 2014403	No relevant outcomes
Levin 2007404	Incorrect interventions
Levin 2015405	Incorrect intervention
Li 2010408	Incorrect interventions
Li 2011406	Diet intervention
Li 2013407	Incorrect interventions
Lin 2014409	Incorrect interventions
Lin 2016410	No useable outcomes
Lin 2017411	No usable outcomes
Lin 2017411	No usable outcomes
Lion-francois 2014412	Not guideline condition
Liu 2011413	Commentary
Logemann 2013415	No relevant outcomes
Loo 2016416	No useable outcomes
Lufi 2007418	Inappropriate washout period
Luman 2015419	No relevant outcomes
Lyon 2010420	Incorrect study design

Study	Exclusion reason
Lyon 2011421	Incorrect interventions
Malone 2009422	Incorrect study design
Manor 2013423	Incorrect interventions
Manor 2014424	Incorrect interventions
Manos 2009425	Inappropriate comparison
Marchant 2010426	Open label
Marchant 2011427	Open label
Marchant 2011428	Inappropriate washout period
Martin 2007430	No useable outcomes
Martin 2014431	Incorrect interventions
Martins 2004432	Inappropriate comparison
Mattes 1984433	Incorrect study design
Mattingly 2012434	Open label
Mattos 2013437	Open label
Mattos 2014436	References checked
Matza 2004439	No data reported
Matza 2007438	Incorrect study design
McCracken 2016440	Incorrect study design
Mcgough 2006441	Inappropriate washout period
Mcgough 2012442	Letter to editor
Mcinnis 2007443	Less than minimum duration
Mcrae-clark 2010444	Incorrect interventions (combined pharma and non-pharma vs. placebo)
Mcrae-clark 2010444	Incorrect interventions (combined pharma and non-pharma vs. placebo)
Mcrae-clark 2010444	Incorrect interventions
Meisel 2013446	Incorrect interventions
Michelson 2002449	Abstract
Michelson 2002449	Abstract
Michelson 2002449	Abstract
Michelson 2002447	Conference abstract
Michelson 2004450	Incorrect interventions
Mikami 2009452	Incorrect interventions
Mikkelsen 1982453	Incorrect study design
Miller 2007454	Inappropriate washout period
Mohammadi 2012458	Incorrect interventions (combination)
Mohammadi 2012458	Incorrect interventions (combination)
Mohammadi 2012458	Incorrect interventions (combination)
Mohammadi 2015457	Incorrect interventions
Monuteaux 2007460	Not licensed in children. Study aim to treat substance use, not ADHD
Moorthy 2015461	Incorrect interventions
Morash-Conway 2016462	Incorrect study design
Moriyama 2013463	Review: references checked
Moshe 2012464	Less than minimum duration
Muir 2010465	No primary research

Study	Exclusion reason
Muniz 2008466	No useable outcomes
Murray 2011467	Incorrect population
Nandam 2011471	No relevant outcomes
Newcorn 2006476	Abstract
Newcorn 2010479	Open label. Add to titration review
Newcorn 2016474	Incorrect population
Ni 2013481	No relevant outcomes
Ni 2016480	Incorrect study design
Niederhofer 2012482	Abstract
Nunes 2013483	No useable outcomes
Ogrim 2013484	Inappropriate comparison
Olsen 2012485	Incorrect interventions
Overtoom 2009487	No relevant outcomes
Owen 2009488	Incorrect population (not ADHD)
Owens 2016489	Incorrect study design
Parker 2013491	Review: references checked
Pataki 1993492	Inappropriate washout period
Pearson 2013494	Incorrect duration
Pelham 2011496	Less than minimum duration. Inappropriate washout period. Treatment duration <2 weeks
Pelham 2014495	Open label dose comparison no washout
Perez-alvarez 2009497	Incorrect interventions
Peterson 2008498	Review: references checked
Philipsen 2014499	Less than minimum duration
Philipsen 2015500	Protocol only
Pierce 2010501	Open label
Pollak 2010503	Less than minimum duration.
Posey 2007504	Inappropriate washout period
Potter 2008506	No relevant outcomes
Potter 2014505	Incorrect intervention
Prada 2015507	Incorrect study design
Prasad 2007509	Open label
Prasad 2009508	Incorrect study design
Prince 2000510	Open label design
Pringsheim 2011511	Cochrane review checked for references
Punja 2012512	Protocol
Ramtvedt 2013514	No relevant outcomes
Ramtvedt 2014513	No relevant outcomes
Ramtvedt 2014515	Incorrect study design. NRS
Rapoport 1974516	Inappropriate method of diagnosis
Rapoport 2008517	Inappropriate washout period
Ray 2009518	Not guideline condition
Redman 2014519	Protocol
Reichow 2013520	Review: references checked
Research units on pediatric psychopharmacology autism	Inappropriate washout period

Study	Exclusion reason
2005522	
Reyes 2006524	Incorrect study design
Rezaei 2010525	Incorrect interventions
Riggs 2011528	Incorrect interventions
Roesch 2013530	Less than minimum duration
Roesch 2013531	Incorrect study design
Rosler 2013533	No relevant outcomes
Rubia 2009535	Inappropriate comparison
Rubia 2011536	No relevant outcomes
Rubia 2011537	No relevant outcomes
Safavi 2016540	Incorrect study design
Sahin 2014541	Incorrect study design
Salehi 2010542	Incorrect interventions
Sallee 2009544	Open label
Sallee 2012543	Review (not systematic)
Sandler 2008546	Incorrect study design
Sandler 2010547	Inappropriate comparison
Santisteban 2014548	No relevant outcomes - sleep
Santosh 2006549	Incorrect study design
Sayer 2016550	Incorrect study design
Schachar 1997555	Incorrect interventions
Schachar 2008554	Less than minimum duration
Schrantee 2016557	Incorrect population
Schulz 2010559	Less than minimum duration.
Schulz 2010558	Inappropriate comparison
Sciberras 2011560	Incorrect interventions
Shakibaei 2015562	Incorrect interventions
Shang 2015563	Open label
Shang 2016564	Incorrect study design
Sharp 1999565	Inappropriate comparison
Shaywitz 2016566	Incorrect study design
Shea 2004567	Incorrect population (not ADHD)
Short 2004568	Incorrect study design
Shytle 2002569	Less than minimum duration
Sikirica 2013570	References checked
Silva 2008574	Less than minimum duration
Silva 2008572	Less than minimum duration
Silva 2013573	Inappropriate comparison
Sinzig 2007577	No useable outcomes
Slama 2015578	No relevant outcomes
Snyder 2002579	Incorrect interventions
So 2008580	Incorrect interventions
Sobanski 2008582	Open label
Sobanski 2012581	Open label
Solanto 2009583	Crossover no washout. Inappropriate washout period

Study	Exclusion reason
Sonuga-barke 2007585	Incorrect duration
Sonuga-barke 2008587	Inappropriate washout period
Sonuga-barke 2009584	Crossover with no washout
Sonuga-barke 2009586	Inappropriate washout period
Spencer 2008594	Incorrect interventions
Spencer 2008595	Incorrect intervention
Spencer 2009588	No useable outcomes
Spencer 2011596	No useable outcomes. Less than minimum duration.
Stein 2011599	Less than minimum duration
Steiner 2014600	Incorrect interventions
Stocks 2012601	Incorrect interventions
Strand 2012602	No relevant outcomes
Stray 2009603	No relevant outcomes
Su 2016604	Incorrect study design
Sung 2010605	Review: references checked
Surman 2010606	Open label
Svanborg 2009609	Incorrect intervention (combination)
Svanborg 2009609	Incorrect intervention (combination)
Svanborg 2009609	Incorrect intervention (combination)
Svanborg 2009608	Incorrect intervention (combination)
Svanborg 2009608	Incorrect intervention (combination)
Svanborg 2009608	Incorrect intervention (combination)
Swanson 2006611	Incorrect population
Swanson 2006610	No relevant outcomes
Swearingen 2007612	Open label
Szobot 2008613	No useable outcomes
Szobot 2008613	No useable outcomes
Szobot 2008613	No useable outcomes
Takahashi 2014615	Studies where response to previous treatment is an inclusion criteria: "Patient were excluded if they were a non-responder to MPH and/or had a history of hypersensitivity or intolerance to MPH"
Tamm 2007617	No relevant outcomes. Less than minimum duration. Incorrect study design
Tamm 2012616	Inappropriate comparison
Taragin 2013618	No relevant outcomes
Tebartz van Elst 2016621	Incorrect study design
Tehrani-doost 2008622	Inappropriate comparison. Less than minimum duration. Open label
Tellechea n 1991623	Inappropriate method of diagnosis
Ter-stepanian 2010625	Crossover no washout
Thomson 2009626	Systematic review checked for references
Thomson 2009627	Systematic review is not relevant to review question or unclear PICO. No ADHD studies. Less than minimum duration
Thurstone 2010628	Incorrect interventions (combination)
Thurstone 2010628	Incorrect interventions (combination)
Thurstone 2010628	Incorrect interventions (combination)

Study	Exclusion reason
Torrioli 2008629	Supplement. Less than minimum duration
Trzepacz 2011633	No relevant outcomes
Tucha 2011634	No relevant outcomes
Upadhyaya 2013635	Studies including participants who have previously received medication for ADHD, or studies where response to previous treatment is an inclusion criteria
Van der donk 2013637	Incorrect interventions
Van der kolk 2014639	Incorrect study design
Van der meer 2013640	Open label
Van der oord 2007642	Incorrect interventions
Van der oord 2008641	Review: references checked
Verster 2008644	Less than minimum duration
Verster 2010645	No relevant outcomes - driving
Warden 2012647	Combination. No relevant outcomes
Waxmonsky 2008648	No useable outcomes
Waxmonsky 2011649	Dose comparison
Waxmonsky 2014650	Studies including participants who have previously received medication for ADHD, or studies where response to previous treatment is an inclusion criteria No washout between open label lead in and double-blind phase
Weber 2008651	Incorrect interventions
Wehmeier 2007653	Single arm open label
Weisler 2009658	Open label, no comparison
Weisler 2012659	Incorrect interventions
Weiss 2004663	Incorrect intervention (wrong drugs)
Weiss 2006660	Incorrect interventions
Weiss 2012661	Incorrect interventions
Wender 2011664	Open label
Werry 1980667	Inappropriate method of diagnosis
Westover 2013668	No relevant outcomes
Wigal 2004672	Inappropriate intervention
Wigal 2005679	Inappropriate intervention
Wigal 2010673	Conference abstract
Wigal 2010677	Less than minimum duration. Inappropriate comparison
Wigal 2010678	no data
Wigal 2010685	Less than minimum duration
Wigal 2011682	Open label trial with two days of randomised, blinded treatment (no washout period stated)
Wigal 2011676	Less than minimum duration
Wigal 2011684	Less than minimum duration
Wigal 2012683	Less than minimum duration. Inappropriate comparison
Wigal 2013674	Less than minimum duration
Wigal 2014675	Studies including participants who have previously received medication for ADHD, or studies where response to previous treatment is an inclusion criteria
Wigal 2015680	Less than minimum duration
Wigal 2016681	Less than minimum duration

Study	Exclusion reason
Wilens 2006693	Incorrect population
Wilens 2008689	Incorrect intervention (wrong drugs)
Wilens 2008692	Inappropriate intervention
Wilens 2008692	Inappropriate intervention
Wilens 2008692	Inappropriate intervention
Wilens 2010691	Inappropriate washout period
Wilens 2011687	No relevant outcomes
Wilens 2012690	Inappropriate intervention
Wilens 2012690	Inappropriate intervention
Williams 2010695	Not relevant
Williamson 2014696	Incorrect study design
Winhusen 2010699	Inappropriate comparison
Winhusen 2010698	Inappropriate comparison
Winhusen 2011697	No outcomes of interest reported
Witt 2008700	Open label
Wong 2012702	Inappropriate comparison
Yang 2012703	Open label
Yang 2015704	Incorrect study design
Yellin am 1978705	Inappropriate method of diagnosis
Yepes 1977706	Inappropriate method of diagnosis
Yildiz 2011707	Open label
Yilmaz 2013708	No relevant outcomes
Young 2014709	No useable outcomes
Zeni 2009712	Incorrect design
Zeni 2009712	Incorrect design
Zheng 2015713	Incorrect design

1

2 I.1.2 Pharmacological sequencing

3

Table 133: Studies excluded from the clinical review

Study	Exclusion reason
Abbasi 2011 ²	Incorrect interventions
Abikoff 2007 ⁴	Less than minimum duration
Abikoff 2009 ³	Crossover no washout, no results reported after 1st phase
Adler 2005 ²²	Inappropriate design
Adler 2008 ¹⁸	Data not fully reported
Adler 2008 ¹⁹	Open label
Adler 2009 ¹⁷	Wrong population
Adler 2009 ¹⁶	Wrong population
Adler 2009 ²¹	Wrong population
Adler 2009 ²⁰	No relevant outcomes: cardio
Adler 2011 ¹³	Incorrect interventions
Adler 2011 ¹⁴	Open label
Adler 2013 ⁸	Wrong population

Study	Exclusion reason
Adler 2013 ⁹	Wrong population
Adler 2014 ⁵	No relevant outcomes
Adler 2014 ⁷	No relevant outcomes
Agay 2010 ²³	No relevant outcomes
Agay 2014 ²⁴	No relevant outcomes
Allen2005 ²⁵	Incorrect comparison
Aman 2000 ³²	Incorrect study design
Aman 2004 ²⁷	Subjects permitted to continue concomitant ADHD medication
Aman 2008 ²⁹	Incorrect study design
Aman 2009 ³³	No control group
Aman 2009 ³⁰	Incorrect comparison (combination)
Aman 2010 ³¹	Wrong population
Aman 2014 ²⁸	Incorrect interventions
Aman 2015 ²⁶	Incorrect study design
Amiri 2008 ³⁵	Incorrect comparison
Amiri 2013 ³⁶	Incorrect study design
An 2013 ³⁷	No relevant outcomes
Anderson 2007 ³⁸	Not article
Anon 2002 ⁶³²	No relevant outcomes
Anon 2002 ⁶³¹	Incorrect study design
Anonymous 2009 ²⁴⁷	Not article
Apostol 2012 ⁴⁰	Incorrect interventions
Arabgol 2015 ⁴¹	Inappropriate comparison
Araki 2015 ⁴²	Inappropriate comparison
Armenteros 2007 ⁴³	Systematic review is not relevant to review question or unclear PICO. no data
Armstrong 2012 ⁴⁴	No relevant outcomes
Arnold 2006 ⁴⁵	Inappropriate comparison
Arnold 2007 ⁴⁶	Incorrect interventions
Arnold 2010 ⁴⁷	Open label
Arnold 2010 ⁴⁸	Original study excluded
Arnold 2015 ⁴⁹	Inappropriate intervention
Asherson 2015 ⁵¹	Systematic review: study designs inappropriate
Ashkenasi 2011 ⁵²	Open label
Babcock 2012 ⁵³	Wrong population
Babinski 2014 ⁵⁴	Incorrect interventions
Babinski 2014 ⁵⁶	Inappropriate intervention
Bahcivan Saydam 2015 ⁵⁷	No intervention
Bain 2012 ⁵⁸	Wrong population
Bain 2013 ⁵⁹	Incorrect interventions
Banaschewski 2013 ⁶¹	Wrong population
Banaschewski 2014 ⁶⁰	Wrong population
Bangs 2007 ⁶²	Inappropriate comparison
Bangs 2008 ⁶³	Abstract
Barbaresi 2014 ⁶⁴	Incorrect study design
Barkley 2007 ⁶⁵	Wrong population

Study	Exclusion reason
Barnard 2002 ⁶⁶	Review: references checked
Barrickman 1995 ⁶⁷	Inappropriate comparison
Bart 2010 ⁶⁹	No relevant outcomes
Bedard 2008 ⁷⁴	No relevant outcomes
Bedard 2015 ⁷³	No relevant outcomes
Bental 2008 ⁷⁶	No relevant outcomes
Benvenuto 2013 ⁷⁷	Incorrect study design
Berlin 2012 ⁷⁸	Incorrect interventions
Biederman 1989 ⁸²	Wrong population
Biederman 1989 ⁸¹	Wrong population
Biederman 1993 ⁸⁰	Wrong population
Biederman 2002 ⁸⁶	Subgroup analysis
Biederman 2005 ⁹⁶	Wrong population
Biederman 2006 ⁹⁵	Wrong population
Biederman 2007 ⁹⁴	Meta-analysis: references checked
Biederman 2007 ⁸⁷	Wrong population
Biederman 2007 ⁸³	Inappropriate intervention
Biederman 2008 ⁹³	Meta-analysis of individual studies included in review
Biederman 2008 ⁸⁸	Open label
Biederman 2008 ⁸⁹	Abstract
Biederman 2012 ⁸⁴	No relevant outcomes
Blader 2009 ⁹⁹	Incorrect interventions
Blader 2013 ⁹⁸	Inappropriate comparison
Block 2009 ¹⁰⁰	Wrong population
Blum 2011 ¹⁰¹	No relevant outcomes
Blumer 2009 ¹⁰²	Incorrect interventions
Boellner 2010 ¹⁰³	Inappropriate comparison
Bögels 2008 ¹⁰⁴	Incorrect interventions
Bohnstedt 2005 ¹⁰⁵	Insufficient information on full trial
Boonstra 2007 ¹⁰⁷	No relevant outcomes
Borsting 2008 ¹⁰⁸	Conference abstract
Bottelier 2014 ¹⁰⁹	Protocol
Bouffard 2003 ¹¹⁰	Crossover with inappropriate washout, no results reported after 1st phase
Brams 2008 ¹¹³	Crossover no washout, less than minimum duration
Brams 2010 ¹¹²	Review: references checked
Brams 2011 ¹¹¹	Open label
Brams 2012 ¹¹⁴	Erratum
Brams 2012 ¹¹⁵	Dose comparison
Brams 2012 ¹¹⁶	No washout following open label lead in phase
Brown 1985	Incorrect study design
Brown 1989 ¹¹⁹	No relevant outcomes
Brown 2006 ¹¹⁸	Inappropriate comparison
Brown 2010 ¹²⁰	Open label
Brown 2010 ¹²²	Summary of 2 included studies
Brown 2011 ¹²¹	Wrong population

Study	Exclusion reason
Bubnik 2015 ¹²³	No relevant outcomes
Buitelaar 1996 ¹³⁰	Inappropriate intervention
Buitelaar 2001 ¹²⁹	Inappropriate comparison
Buitelaar 2007 ¹²⁶	Wrong population
Buitelaar 2009 ¹²⁷	Open label
Buitelaar 2012 ¹²⁸	Open label
Burton 2015 ¹³¹	Not guideline condition
Butter 1983 ¹³²	Less than minimum duration
Butter 1984 ¹³³	Less than minimum duration
Camporeale 2013 ¹³⁵	Wrong population
Cantilena 2012 ¹³⁷	No relevant outcomes
Cardo 2013 ¹³⁸	Open label
Casas 2013 ¹⁴⁰	Wrong population
Cetin 2015 ¹⁴⁵	Open label
Chang 2009 ¹⁴⁷	Open label
Chang 2012 ¹⁴⁸	No relevant outcomes
Chantiluke 2015 ¹⁴⁹	No relevant outcomes
Chantiluke 2015 ¹⁵⁰	Incorrect study design
Chavez 2006 ¹⁵¹	Review: references checked
Chen 2014 ¹⁵²	Wrong population
Cheng-shannon 2004 ¹⁵³	Review: references checked
Childress 2009 ¹⁵⁸	Inappropriate intervention
Childress 2014 ¹⁵⁵	Wrong population
Childress 2014 ¹⁵⁷	No comparator
Childress 2015 ¹⁵⁶	Inappropriate intervention
Cho 2011 ¹⁶⁰	Open label
Chronis-tuscano 2008 ¹⁶²	Inappropriate washout period after lead in
Classen 2013 ¹⁶³	Systematic review: study designs inappropriate
Classen 2013 ¹⁶⁴	Incorrect study design
Classen 2013 ¹⁶⁵	Incorrect study design
Coghill 2007 ¹⁷²	Crossover no washout period, no results reported after 1st phase
Coghill 2013 ¹⁶⁷	Wrong population
Coghill 2014 ¹⁶⁹	Systematic review: study designs inappropriate. open label
Coghill 2014 ¹⁷⁰	Wrong population
Coghill 2014 ¹⁷¹	Wrong population
Cohen-yavin 2009 ¹⁷³	Open label
Collins 2013 ¹⁷⁴	Not article
Comer 2013 ¹⁷⁵	Incorrect interventions
Connor 1994 ¹⁷⁹	Incorrect study design
Connor 2013 ¹⁸²	Open label
Connor 2014 ¹⁸⁰	References checked
Corkum 2008 ¹⁸³	Crossover no washout, less than minimum duration
Cornforth 2010 ¹⁸⁴	Review: references checked
Correia Filho 2005 ¹⁸⁵	Inappropriate method of diagnosis
Cortese 2012 ¹⁸⁶	No outcomes of interest

Study	Exclusion reason
Costa 2013 ¹⁸⁷	No relevant outcomes
Covey 2010 ¹⁹¹	Inappropriate comparison
Covey 2011 ¹⁸⁹	No relevant outcomes
Covey 2015 ¹⁹⁰	No data (whole sample only no comparison)
Cox 2008 ¹⁹³	No relevant outcomes
Cox 2012 ¹⁹²	Open label
Cubillo 2014 ¹⁹⁴	No relevant outcomes
Cubillo 2014 ¹⁹⁵	No relevant outcomes
Cutler 2015 ¹⁹⁶	Conference abstract
Dean 2011 ²⁰¹	Inappropriate design
Devito 2009 ²⁰⁴	Incorrect study design
Dinca 2005 ²⁰⁵	Review: references checked
Dittmann 2009 ²⁰⁹	Open label
Doig 2008 ²¹⁰	Incorrect study design
Donnelly 1986 ²¹²	Incorrect interventions: all participants using a monoamine diet and engaged in a behavioural intervention during the study. To be added to combination review.
Dopfner 2011 ²¹³	Wrong population
Durell 2014 ²¹⁷	Erratum
DuPaul 2012 ²¹⁴	Inappropriate design
Epstein 2011 ²¹⁹	Inappropriate washout period, less than minimum duration
Fabiano 2007 ²²²	Inappropriate intervention
Farah 2009 ²²⁴	No relevant outcomes
Farah 2009 ²²³	No relevant outcomes
Faraone 2007 ²²⁹	Inappropriate intervention
Faraone 2009 ²²⁵	Review: references checked
Faraone 2009 ²²⁷	No data to extract
Faraone 2010 ²²⁶	Review: references checked
Faraone 2012 ²²⁸	Dose comparison
Farmer 2015 ²³⁰	Inappropriate intervention
Fernandez-jaen 2013 ²³²	Not RCT
Findling 2007 ²⁴²	crossover with no washout, less than minimum duration
Findling 2006 ²⁴¹	Wrong population
Findling 2008 ²³⁴	Wrong population
Findling 2008 ²³⁵	Not article
Findling 2008 ²³⁷	Open label
Findling 2009 ²⁴⁴	Open label
Findling 2010 ²³⁹	Open label
Findling 2010202	Summary of two excluded papers
Findling 2011 ²³⁶	Wrong population
Findling 2013 ²³⁸	No comparator
Findling 2014 ²⁴⁰	Combination of drugs
Fitzpatrick 1990 ²⁴⁵	Not article (thesis)
Flapper 2008 ²⁴⁶	Open label
Foster 2007 ²⁴⁹	Inappropriate intervention
Fox 2014 ²⁵⁰	No relevant outcomes

Study	Exclusion reason
Fredriksen 2014 ²⁵¹	Open label
Froehlich 2011 ²⁵³	no outcomes of interest reported
Froehlich 2014 ²⁵²	Less than minimum duration
Fuentes 2013 ²⁵⁴	Open label
Fung 2016 ²⁵⁵	Review: references checked
Gadow 2008 ²⁵⁹	Inappropriate washout
Gadow 2011 ²⁵⁸	Incorrect study design
Gallucci 2006 ²⁶²	Incorrect study design
Garfinkel 1983 ²⁶³	Inappropriate intervention
Garg 2014 ²⁶⁴	Open label
Garg 2015 ²⁶⁵	Open label
Gau 2010 ²⁶⁷	Open label
Gehricke 2009 ²⁶⁹	Incorrect interventions
Gehricke 2011 ²⁷⁰	Incorrect study design
Geller 2007 ⁵⁷	Inappropriate washout prior to study
Ghanizadeh 2012 ²⁷²	Incorrect intervention (combination)
Ghanizadeh 2013 ²⁷³	Incorrect interventions
Ghuman 2007 ²⁷⁵	Crossover no washout, less than minimum duration
Ghuman 2009 ²⁷⁴	Wrong population
Giblin 2011 ²⁷⁶	No washout after lead in
Ginsberg 2011 ²⁷⁸	Open label
Ginsberg 2012 ²⁸⁰	Open label
Ginsberg 2014 ²⁷⁹	Open label
Gittelman-Klein 1976 ²⁸²	Inappropriate diagnosis method (DSM-II)
Goez 2012 ²⁸³	No data
Gonzalez-heydrich 2010 ²⁸⁵	Less than minimum duration
Grant 2015 ²⁸⁸	Conference abstract
Green 2011 ²⁸⁹	Less than minimum duration
Greenhill 2002 ²⁹²	Wrong population
Greenhill 2003 ²⁹⁴	Inappropriate intervention
Greenhill 2006 ²⁹¹	Wrong population
Greenhill 2006 ²⁹⁰	Wrong population
Greenhill 2006 ²⁹³	Wrong population
Grizenko 2010 ²⁹⁶	Wrong population
Grizenko 2012 ²⁹⁷	Wrong population
Grizenko 2013 ²⁹⁵	Less than minimum duration
Groom 2013 ²⁹⁵	Inappropriate comparison
Guardiola 1999 ²⁹⁹	Not in English
Gunther 2010 ³⁰⁰	No relevant outcomes
Guo 2013 ³⁰¹	Conference abstract
Gustafsson 2010 ³⁰²	Incorrect interventions
Haas 2008 ³⁰³	Open label
Haghighat 2014 ³⁰⁴	Not article
Hammerness 2009 ³⁰⁷	Review: references checked
Hammerness 2013 ³⁰⁶	Open label

Study	Exclusion reason
Handen 2000 ³⁰⁹	Inappropriate washout period
Handen 2011 ³¹¹	Incorrect study design, less than minimum duration
Hardan 2005 ³¹²	Inappropriate design
Harfterkamp 2013 ³¹³	Open label
Harfterkamp 2015 ³¹⁶	Open label
Hazell 2003 ³¹⁹	Combination intervention
Hazell 2006 ³¹⁸	Wrong population
Hazell 2009 ³¹⁷	Incorrect comparison
Heffner 2013 ³²⁰	No relevant outcomes
Hellwig-bridia 2011 ³²¹	No relevant outcomes
Helseth 2015 ³²²	Incorrect study design
Heriot 2008 ³²³	Inappropriate intervention
Hervas 2014 ³²⁵	Inappropriate method of diagnosis
Hester 2010 ³²⁶	No relevant outcomes
Hilton 2013 ³²⁷	Not guideline condition
Hirata 2014 ³²⁸	Incorrect study design
Hoebert 2009 ³²⁹	Incorrect study design
Holden 2013 ³³⁰	Not guideline condition (cost data)
Hong 2009 ³³¹	Incorrect comparison
Hong 2014 ³³²	Inappropriate comparison
Hosenbocus 2009 ³³³	Review: references checked
Howard 2015 ³³⁴	Inappropriate intervention
Hurt 2011 ³³⁶	Non-ADHD population
Hurwitz 2012 ³³⁷	Systematic review: study designs inappropriate
Huss 2014 ³³⁸	Open label
Huss 2014 ³³⁹	Wrong population
Ialongo 1994 ³⁴¹	Incorrect study design
Ironside 2010 ³⁴²	No relevant outcomes
Ishii-takahashi 2015 ³⁴³	Correction
Jacobi-polishook 2009 ³⁴⁴	No relevant outcomes
Jahromi 2009 ³⁴⁷	Inappropriate washout period, less than minimum duration
Jain 2007 ³⁵¹	Wrong population
Jain 2013 ³⁴⁹	Systematic review: study designs inappropriate
Jans 2012 ³⁵²	Inappropriate intervention
Jaselskis 1992 ³⁵³	Population defined as previously non-responsive to heterogenous treatments
Jasinski 2008 ³⁵⁴	Inappropriate washout period, non-ADHD population
Jasinski 2009 ³⁵⁵	No relevant outcomes
Jin 2013 ³⁵⁷	Open label
Johnston 2014 ³⁵⁸	Incorrect interventions
Jordan 2012 ³⁵⁹	Incorrect study design
Jucaite 2014 ³⁶⁰	Incorrect interventions
Kaplan 2004 ³⁶³	Subgroup analysis
Kay 2009 ³⁶⁴	Wrong population
Keating 2011 ³⁶⁵	Not article
Kent 2013 ³⁶⁷	Open label

Study	Exclusion reason
Keulers 2007 ³⁶⁸	Open label
Khodadust 2012 ³⁶⁹	Incorrect intervention
Kim 2009 ³⁷⁰	Open label
King 2009 ³⁷²	Less than minimum duration
Koblan 2015 ³⁷³	Incorrect intervention
Kollins 2006 ³⁷⁴	Wrong population
Kollins 2009 ³⁷⁵	No relevant outcomes
Kollins 2013 ³⁷⁹	ADHD vs non ADHD population
Kollins 2014 ³⁷⁶	ADHD vs non ADHD population
Konstenius 2010 ³⁸¹	Inappropriate intervention
Konstenius 2013 ³⁸⁴	No means given
Konstenius 2014 ³⁸²	No means given
Kooij 2013 ³⁸⁶	No relevant outcomes - adherence
Krakowski 1965 ³⁸⁷	Inappropriate method of diagnosis (before date cut off)
Kratochvil 2007 ³⁸⁸	Inappropriate design
Kratochvil 2011 ³⁹⁰	Incorrect comparison
Kubas 2012 ³⁹¹	No relevant outcomes
Kupietz 1988 ³⁹³	Participants were excluded from trial after randomisation if they did not respond to treatment or if they experienced side effects
Law 1999 ³⁹⁶	Inappropriate intervention
LeBlanc 2005 ³⁹⁷	Subjects permitted to continue concomitant ADHD medication
Leddy 2009 ³⁹⁸	Genetics
Lee 2013 ³⁹⁹	No relevant outcomes
Lerer 1977 ⁴⁰²	Inappropriate washout period, no relevant outcomes
Lerer 1979 ⁴⁰¹	Inappropriate washout period, no relevant outcomes
Leuchter 2014 ⁴⁰³	No relevant outcomes
Levin 2007 ⁴⁰⁴	Inappropriate intervention – Non-pharma + Pharma
Levin 2015 ⁴⁰⁵	Incorrect interventions
Li 2010 ⁴⁰⁸	Inappropriate intervention
Li 2011 ⁴⁰⁶	Incorrect intervention
Li 2013 ⁴⁰⁷	Incorrect interventions
Lin 2014 ⁴⁰⁹	Incorrect interventions
Lion-francois 2014 ⁴¹²	Not guideline condition
Liu 2011 ⁴¹³	Commentary
Logemann 2013 ⁴¹⁵	No relevant outcomes
Lopez 2008 ⁴¹⁷	Wrong population
Lufi 2007 ⁴¹⁸	Crossover no washout, no results reported after 1st phase
Luman 2015 ⁴¹⁹	No relevant outcomes
Lyon 2010 ⁴²⁰	Incorrect study design
Lyon 2011 ⁴²¹	Incorrect interventions
Malone 2009 ⁴²²	Incorrect study design
Manor 2013 ⁴²³	Incorrect interventions
Manor 2014 ⁴²⁴	Incorrect interventions
Manos 2009 ⁴²⁵	Inappropriate comparison
Marchant 2010 ⁴²⁶	Open label
Marchant 2011 ⁴²⁷	Open label

Study	Exclusion reason
Marchant 2011 ⁴²⁸	Inappropriate washout period, no results reported after 1st phase
Martin 2007 ⁴³⁰	Systematic review is not relevant to review question or unclear PICO. Data in graphs with no SDs
Martin 2014 ⁴³¹	Incorrect interventions
Martins 2004 ⁴³²	Inappropriate interventions
Mattes 1984 ⁴³³	Incorrect study design
Mattingly 2012 ⁴³⁴	Open label
Mattos 2013 ⁴³⁷	Open label
Mattos 2014 ⁴³⁶	Review: references checked
Matza 2004 ⁴³⁹	No data reported
Mcgough 2006 ⁴⁴¹	Inappropriate washout period, less than minimum duration
Mcgough 2012 ⁴⁴²	Letter to editor
Mcinnis 2007 ⁴⁴³	Less than minimum duration
Mcrae-clark 2010 ⁴⁴⁴	Incorrect interventions (combined pharma and non-pharma vs. placebo)
Medori 2008 ⁴⁴⁵	Wrong population
Meisel 2013 ⁴⁴⁶	Incorrect interventions
Michelson 2002 ⁴⁴⁷	Conference abstract
Michelson 2003 ⁴⁴⁸	Studies where response to previous treatment is an inclusion criteria
Michelson 2004 ⁴⁵⁰	Wrong population
Mikami 2009 ⁴⁵²	Wrong population
Mikkelsen 1982 ⁴⁵³	Incorrect study design
Miller 2007 ⁴⁵⁴	Inappropriate washout period, less than minimum duration
Mohammadi 2012 ⁴⁵⁸	Incorrect interventions (combination)
Mohammadi 2015 ⁴⁵⁷	Incorrect interventions
Monuteaux 2007 ⁴⁶⁰	Incorrect interventions
Moriyama 2013 ⁴⁶³	Review: references checked
Moshe 2012 ⁴⁶⁴	Less than minimum duration
Muir 2010 ⁴⁶⁵	No primary research
Muniz 2008 ⁴⁶⁶	No variability data
Murray 2011 ⁴⁶⁷	Wrong population
Nandam 2011 ⁴⁷¹	No relevant outcomes
Newcorn 2006 ⁴⁷⁶	Abstract
Newcorn 2008 ⁴⁷⁵	Wrong population
Newcorn 2010 ⁴⁷⁹	Open label
Ni 2013 ⁴⁸¹	No relevant outcomes
Niederhofer 2012 ⁴⁸²	Abstract
Nunes 2013 ⁴⁸³	Outcomes not fully reported
Olsen 2012 ⁴⁸⁵	Inappropriate washout period, no results reported after 1st phase
Overtoom 2009 ⁴⁸⁷	No relevant outcomes
Owen 2009 ⁴⁸⁸	Wrong population
Parker 2013 ⁴⁹¹	Review: references checked
Pataki 1993 ⁴⁹²	Crossover no washout, no results reported after 1st phase
Pearson 2013 ⁴⁹⁴	Less than minimum duration
Pelham 2011 ⁴⁹⁶	Inappropriate washout period

Study	Exclusion reason
Pelham 2014 ⁴⁹⁵	Open label dose comparison no washout
Perez-alvarez 2009 ⁴⁹⁷	Incorrect interventions
Peterson 2008 ⁴⁹⁸	Review: references checked
Philipsen 2014 ⁴⁹⁹	Less than minimum duration
Philipsen 2015 ⁵⁰⁰	Inappropriate intervention
Pierce 2010 ⁵⁰¹	Open label
Pollack 2010 ⁵⁰³	No relevant outcomes
Posey 2007 ⁵⁰⁴	Inappropriate washout period, less than minimum duration
Potter 2008 ⁵⁰⁶	Less than minimum duration
Potter 2014 ⁵⁰⁵	Incorrect interventions
Prada 2015 ⁵⁰⁷	Incorrect study design
Prasad 2007 ⁵⁰⁹	Open label
Prince 2000 ⁵¹⁰	Participants were excluded from trial after randomisation if they did not respond to treatment or if they experienced side effects
Pringsheim 2011 ⁵¹¹	Cochrane review: checked for references
Punja 2012 ⁵¹²	Protocol
Ramtvedt 2013 ⁵¹⁴	Crossover no washout, no results reported after 1st phase
Ramtvedt 2014 ⁵¹³	Crossover no washout, no results reported after 1st phase
Ramtvedt 2014 ⁵¹⁵	Incorrect study design
Rapoport 1975 ⁵¹⁶	Inappropriate method of diagnosis: no ADHD diagnosis
Rapport 2008 ⁵¹⁷	Inappropriate washout period, less than minimum duration
Ray 2009 ⁵¹⁸	Not guideline condition
Redman 2014 ⁵¹⁹	Protocol
Reichow 2013 ⁵²⁰	Review: references checked
Reimherr 2007 ⁵²¹	Inappropriate washout period, no results reported after 1st phase
Research units on pediatric psychopharmacology autism 2005 ⁵²²	Inappropriate washout period, less than minimum duration
Reyes 2006 ⁵²⁴	Not guideline condition
Rezaei 2010 ⁵²⁵	Incorrect interventions (combination trial)
Riahi 2010 ⁵²⁶	Crossover no washout, no results reported after 1st phase
Richardson 1988 ⁵²⁷	Participants were excluded from trial after randomisation if they did not respond to treatment or if they experienced side effects
Riggs 2011 ⁵²⁸	Inappropriate intervention
Robison 2010 ⁵²⁹	Crossover no washout, no results reported after 1st phase
Roesch 2013 ⁵³⁰	Less than minimum duration
Roesch 2013 ⁵³¹	Incorrect study design
Rosler 2013 ⁵³³	Wrong population
Rubia 2009 ⁵³⁵	Inappropriate comparison
Rubia 2011 ⁵³⁶	No relevant outcomes
Rubia 2011 ⁵³⁷	No relevant outcomes
Sahin 2014 ⁵⁴¹	Incorrect study design
Salehi 2010 ⁵⁴²	Incorrect interventions
Sallee 2009 ⁵⁴⁴	Open label
Sallee 2009 ⁵⁴⁵	Wrong population
Sallee 2012 ⁵⁴³	Re-analysis of 2 studies excluded from the review

Study	Exclusion reason
Sandler 2008 ⁵⁴⁶	Incorrect study design
Sandler 2010 ⁵⁴⁷	Inappropriate comparison
Santisteban 2014 ⁵⁴⁸	No relevant outcomes
Santosh 2006 ⁵⁴⁹	Incorrect study design
Saylor 2010 ⁵⁵¹	Inappropriate comparison
Schachar 1997 ⁵⁵⁵	Inappropriate intervention
Schachar 2008 ⁵⁵⁴	Less than minimum duration
Schulz 2010 ⁵⁵⁹	Less than minimum duration
Schulz 2010 ⁵⁵⁸	Inappropriate comparison
Shakibaei 2015 ⁵⁶²	Incorrect interventions
Shang 2015 ⁵⁶³	Open label
Sharp 1999 ⁵⁶⁵	Inappropriate comparison
Shea 2004 ⁵⁶⁷	Wrong population
Short 2004	Incorrect study design
Shytle 2002 ⁵⁶⁹	Less than minimum duration
Sikirica 2013 ⁵⁷⁰	Review: references checked
Silva 2013 ⁵⁷³	Dose comparison
Sinzig 2007 ⁵⁷⁷	Systematic review is not relevant to review question or unclear PICO. papers needed with results are in German
Slama 2015 ⁵⁷⁸	No relevant outcomes
Snyder 2002 ⁵⁷⁹	Subjects permitted to continue concomitant ADHD medication
So 2008 ⁵⁸⁰	Inappropriate intervention
Sobanski 2008 ⁵⁸²	Open label
Sobanski 2012 ⁵⁸¹	Open label drug vs. placebo
Solanto 2009 ⁵⁸³	Crossover no washout
Sonuga-barke 2007 ⁵⁸⁵	Wrong population
Sonuga-barke 2008 ⁵⁸⁷	Crossover with no washout
Sonuga-barke 2009 ⁵⁸⁴	Less than minimum duration
Sonuga-barke 2009 ⁵⁸⁶	Less than minimum duration
Spencer 2007 ⁵⁹³	Wrong population
Spencer 2008 ⁵⁹⁴	Incorrect interventions
Spencer 2008 ⁵⁹⁵	Drug not licensed
Spencer 2009 ⁵⁸⁸	No data
Spencer 2011 ⁵⁹⁶	Systematic review is not relevant to review question or unclear PICO. outcomes not fully reported
Stein 2011 ⁵⁹⁹	Less than minimum duration
Steiner 2014 ⁶⁰⁰	Incorrect interventions
Stocks 2012 ⁶⁰¹	Drug not licensed
Strand 2012 ⁶⁰²	No relevant outcomes
Stray 2009 ⁶⁰³	No relevant outcomes
Sung 2010 ⁶⁰⁵	Review: references checked
Surman 2010 ⁶⁰⁶	Open label
Swanson 2006 ⁶¹¹	Wrong population
Swanson 2006 ⁶¹⁰	No relevant outcomes
Swearingen 2007 ⁶¹²	Open label
Szobot 2008 ⁶¹³	Crossover no washout, results not reported after 1st phase

Study	Exclusion reason
Takahashi 2014 ⁶¹⁴	Wrong population
Takahashi 2014 ⁶¹⁵	Wrong population
Tamm 2007 ⁶¹⁷	No relevant outcomes
Tamm 2012 ⁶¹⁶	Inappropriate intervention
Taragin 2013 ⁶¹⁸	No relevant outcomes
Taylor 2000 ⁶¹⁹	Crossover inappropriate washout, no results reported after 1st phase
Taylor 2001 ⁶²⁰	Crossover inappropriate washout, no results reported after 1st phase
Tehrani-doost 2008 ⁶²²	Inappropriate comparison. Open label
Tellechea n 1991 ⁶²³	Inappropriate diagnosis method (no information provided)
Ter-stepanian 2010 ⁶²⁵	Less than minimum duration
The MTA Cooperative Group 1999 ¹	Inappropriate interventions
Thomson 2009 ⁶²⁷	Systematic review is not relevant to review question or unclear PICO: no ADHD studies.
Thurstone 2010 ⁶²⁸	Incorrect interventions (combination)
Torrioli 2008 ⁶²⁹	Incorrect interventions
Trzepacz 2011 ⁶³³	No relevant outcomes
Tucha 2011 ⁶³⁴	No relevant outcomes
Upadhyaya 2013 ⁶³⁵	Wrong population
Upadhyaya 2015 ⁶³⁶	No relevant outcomes. Add to stopping review
Van der meer 2013 ⁶⁴⁰	Open label study
Van der oord 2007 ⁶⁴²	Inappropriate intervention
Van der oord 2008 ⁶⁴¹	Review: references checked
Verster 2008 ⁶⁴⁴	No relevant outcomes
Verster 2010 ⁶⁴⁵	No relevant outcomes
Warden 2012 ⁶⁴⁷	Inappropriate intervention
Waxmonsky 2008 ⁶⁴⁸	No data - 4 arms reported together
Waxmonsky 2011 ⁶⁴⁹	Dose comparison
Waxmonsky 2014 ⁶⁵⁰	No washout between open label lead in and double-blind phase
Weber 2008 ⁶⁵¹	Incorrect interventions
Wehmeier 2007 ⁶⁵³	Single arm open label
Wehmeier 2011 ⁶⁵⁵	Single arm open label, no comparison
Weisler 2009 ⁶⁵⁸	Open label, no comparison
Weisler 2012 ⁶⁵⁹	Wrong population
Weiss 2004 ⁶⁶³	Inappropriate intervention
Weiss 2005 ⁶⁶²	Inappropriate comparison
Weiss 2006 ⁶⁶⁰	Inappropriate intervention
Weiss 2012 ⁶⁶¹	Inappropriate intervention
Wender 2011 ⁶⁶⁴	Open label
Werry 1979 ⁶⁶⁷	Inappropriate method of diagnosis (before date cut off)
Westover 2013 ⁶⁶⁸	No relevant outcomes - cardio
Wigal 2004 ⁶⁷²	Inappropriate intervention
Wigal 2005 ⁶⁷⁹	Inappropriate intervention
Wigal 2006 ⁶⁸⁶	No results reported

Study	Exclusion reason
Wigal 2010 ⁶⁷³	Conference abstract
Wigal 2010 ⁶⁷⁷	Inappropriate comparison
Wigal 2010 ⁶⁷⁸	No data
Wigal 2010 ⁶⁸⁵	Wrong population
Wigal 2011 ⁶⁸²	Open label trial with two days of randomised, blinded treatment (no washout period stated)
Wigal 2011 ⁶⁸⁴	Wrong population
Wigal 2011 ⁶⁷⁶	Wrong population
Wigal 2012 ⁶⁸³	Inappropriate comparison
Wigal 2013 ⁶⁷⁴	Less than minimum duration
Wigal 2015 ⁶⁸⁰	Less than minimum duration
Wilens 2006 ⁶⁹³	Wrong population
Wilens 2008 ⁶⁹²	Inappropriate intervention
Wilens 2008 ⁶⁸⁹	Wrong population
Wilens 2010 ⁶⁹¹	Inappropriate washout period, results not reported after first phase
Wilens 2011 ⁶⁸⁷	No relevant outcomes
Williams 2010 ⁶⁹⁵	Not relevant
Williamson 2014 ⁶⁹⁶	Less than minimum duration
Winhusen 2010 ⁶⁹⁹	Inappropriate comparison
Winhusen 2010 ⁶⁹⁸	Inappropriate comparison
Winhusen 2011 ⁶⁹⁷	No outcomes of interest reported
Witt 2008 ⁷⁰⁰	Open label
Wolraich 2001 ⁷⁰¹	Wrong population
Wong 2012 ⁷⁰²	No relevant outcomes
Yang 2012 ⁷⁰³	Open label
Yang 2015 ⁷⁰⁴	Incorrect study design
Yellin 1978 ⁷⁰⁵	Inappropriate method of diagnosis (before date cut off)
Yepes 1976 ⁷⁰⁶	Inappropriate method of diagnosis (DSM-II)
Yildiz 2011 ⁷⁰⁷	Open label
Yilmaz 2013 ⁷⁰⁸	No relevant outcomes
Young 2014 ⁷⁰⁹	Systematic review is not relevant to review question or unclear PICO
Zheng 2015 ⁷¹³	Inappropriate comparison: ADHD vs non ADHD

1 I.2 Excluded health economic studies

2 I.2.1 Pharmacological efficacy

3 **Table 134: Studies excluded from the health economic review**

Reference	Reason for exclusion
Donnelly 2004 ²¹¹	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 and there is other evidence that is therefore more applicable.
Gilmore & Milne 2001 ²⁷⁷	This study was assessed as not applicable because the cost year is 1997 and it is therefore before the guideline date cut-off.

Reference	Reason for exclusion
	The measure used to generate QALY's (IHRQL) is also not a measure commonly used by NICE.
The MTA Co-operative study Jensen et al., 2005 Foster et al., 2007 ²⁴⁹	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 CIS-ES).
Narayan & Hay 2004 ⁴⁷²	This study was assessed as not applicable because it is a US study and there may be more applicable evidence. The measure used to generate QALY's (IHRQL) is also not a measure commonly used by NICE.
Zupancic 1998 ⁷¹⁷	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)

1 **I.2.2 Pharmacological sequencing**

2 None

3

Appendix J: Research recommendations

J.1 Medication choice in people with co-existing conditions

Research question: What is the clinical and cost effectiveness of ADHD medications in people with ADHD and tic disorders, a history of psychosis or mania, or emotional dysregulation?

Why this is important:

This guideline did not identify any evidence to justify different medication choices in the groups with ADHD and tic disorders, a history of psychosis or mania, or emotional dysregulation. These groups are often excluded from trials. There are reasons (for example, mechanism of action of medication options, previous reports of adverse events) to suspect that these groups may respond differently to different drugs but a lack of trials to confirm this. Primarily there are some concerns that stimulant medication may worsen the symptoms of any of these co-existing conditions and therefore non-stimulant medication should be preferred.

Criteria for selecting high-priority research recommendations:

PICO question	<p>Population:</p> <ul style="list-style-type: none"> • Children, young people and adults with ADHD and tic disorders • Children, young people and adults with ADHD and history of psychosis/mania • Children, young people and adults with ADHD and emotional dysregulation <p>Intervention(s): stimulant medication (methylphenidate, lisdexamfetamine, dexamphetamine)</p> <p>Comparison: non-stimulant medication (atomoxetine, guanfacine), placebo</p> <p>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, co-existing condition specific outcomes (e.g. emotional dysregulation, tics, psychotic episodes), discontinuations, serious adverse events</p>
Importance to patients or the population	Potential to improve care of people with ADHD and these co-morbidities (reduce unnecessary adverse events, allow for most efficient prescribing)
Relevance to NICE guidance	Allow for update and changes to recommendations on prescribing for people with ADHD and co-existing conditions
Relevance to the NHS	Potential to improve care of people with ADHD and these co-morbidities (reduce unnecessary adverse events, allow for most efficient prescribing)
National priorities	NICE ADHD guideline
Current evidence base	<p>Very little evidence in any of these specific subgroups and if any available, principally comparing one medication with placebo as opposed to head to head comparisons</p> <p>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.</p>
Equality	Research would reduce inequality in people with co-existing conditions receiving inappropriate care
Study design	RCT
Feasibility	N/A

Other comments	Currently there are no trials that have selected ADHD patients for high levels of emotional dysregulation or comorbidity with other mental health disorders in which chronic symptoms of emotional dysregulation are prominent. There is an ongoing trial funded by EME (NIHR/MRC) that is investigating the effects of oros-methylphenidate in young adult offenders aged 16-25 in which ADHD is the primary outcome, and there is no selection for high levels of emotional dysregulation at baseline.
Importance	<ul style="list-style-type: none"> High: the research is essential to inform future updates of key recommendations in the guideline.

1 **J.2 Medication choice in people with no previous medication** 2 **for ADHD**

3 **Research question: What is the clinical and cost effectiveness of ADHD medications**
 4 **in people with ADHD with no previous medication for the condition?**

5 **Why this is important:**

6 This guideline makes recommendations for the medication choices for people with ADHD,
 7 but most of the evidence to support these recommendations comes from studies in people
 8 who have previously received medication. Therefore, these studies often include a
 9 population not representative of the people with newly diagnosed ADHD. There may be
 10 differing levels of efficacy of the various treatment options in this population.

11 **Criteria for selecting high-priority research recommendations:**

PICO question	Population: children, young people and adults with ADHD who have never previously used ADHD medication Intervention(s): methylphenidate, lisdexamfetamine, dexamphetamine, atomoxetine, guanfacine Comparison: placebo and each other 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	Potential to improve care of people with ADHD by optimising medication choices
Relevance to NICE guidance	Allow for update and changes to recommendations on prescribing for people with ADHD
Relevance to the NHS	Potential to improve care of people with ADHD by optimising medication choices
National priorities	NICE ADHD guideline
Current evidence base	Little evidence available in the truly medication naïve. 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	N/A
Study design	RCT
Feasibility	N/A
Other comments	N/A
Importance	<ul style="list-style-type: none"> High: the research is essential to inform future updates of key recommendations in the guideline.

1 J.3 Prescribing beyond monotherapy

2 **Research question: What is the clinical and cost effectiveness of various ADHD**
 3 **prescribing strategies when monotherapy has failed?**

4 **Why this is important:**

5 This guideline makes recommendations for the medication choices for people with ADHD up
 6 to the point at which common monotherapies are exhausted. There is very little evidence to
 7 guide healthcare professionals beyond this point, particularly with regards to whether there is
 8 a benefit of prescribing stimulant and non-stimulant medication together.

9 **Criteria for selecting high-priority research recommendations:**

PICO question	Population: children, young people and adults with ADHD whose symptoms persist despite trials of at least one stimulant (e.g. methylphenidate, lisdexamfetamine, dexamphetamine) and one non stimulant (e.g. guanfacine, atomoxetine) Intervention(s): stimulant + non-stimulant (e.g. methylphenidate + atomoxetine), stimulant/non-stimulant + placebo Comparison: each other 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	Combination treatment (methylphenidate and atomoxetine) is frequently used in patients who failed to response to monotherapy. However, there is no evidence to support such practice
Relevance to NICE guidance	Allow for update and changes to recommendations on prescribing for people with ADHD
Relevance to the NHS	Patients with severe uncontrolled ADHD symptoms usually require frequent medical consultation and care. If dual therapy is proven to be appropriate, it is likely to reduce consultation and ADHD-related injury of this high-risk group. On the other hand, dual therapy is likely to cause more adverse effects; hence this trial will also provide evidence to measure and manage such adverse events
National priorities	NICE ADHD guideline
Current evidence base	Currently there is no evidence to support the efficacy, safety, acceptance and cost effectiveness of combination treatments 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	N/A
Study design	RCT, minimum follow-up 12 months, some measures will be needed to confirm that people are non-responsive to previous medication (e.g. titration/run-in period)
Feasibility	N/A
Other comments	N/A
Importance	<ul style="list-style-type: none"> • High: the research is essential to inform future updates of key recommendations in the guideline.

10